

# CHLOROFORM

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A guideline value for chloroform of 200 µg/litre was established in the 1993 WHO *Guidelines for drinking-water quality*. The guideline value was based on extrapolation of an observed increase in kidney tumours in male rats exposed to chloroform in drinking-water for 2 years, although it was recognized that chloroform may induce tumours through a non-genotoxic mechanism. The guideline value was calculated using the linearized multistage model to correspond with a  $10^{-5}$  excess lifetime cancer risk.

Because of the increasing database on mechanisms of induction of tumours by chloroform and because an IPCS Environmental Health Criteria monograph on chloroform was published in 1994, the Coordinating Committee for the updating of the WHO *Guidelines* recommended that chloroform be re-evaluated for the 1998 Addendum.

## 1. GENERAL DESCRIPTION

### 1.1 Identity

CAS no: 67-66-3  
Molecular formula:  $\text{CHCl}_3$

Chloroform is the most commonly occurring trihalomethane (THM); THMs are halogen-substituted single-carbon compounds with the general formula  $\text{CHX}_3$ .

### 1.2 Physicochemical properties<sup>1</sup>

Chloroform is degraded photochemically, is not flammable, and is soluble in most organic solvents. However, its solubility in water is limited. Phosgene and hydrochloric acid may be formed by chemical degradation. The most important physical properties of chloroform are presented below (IARC, 1979; Budvari et al., 1989).

<i>Property</i>	<i>Value</i>
Physical state	Clear, colourless liquid
Boiling point at 101.3 kPa	61.3°C
Melting point	-63.2°C

<sup>1</sup> Conversion factor in air:  $1 \text{ mg/m}^3 = 0.20 \text{ ppm}$ .

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<i>Property</i>	<i>Value</i>
Relative density (20°C)	1.484
Auto-ignition temperature	>1000°C
Water solubility (25°C)	7.5–9.3 g/litre
Vapour density (101.3 kPa, 0°C)	4.36 kg/m <sup>3</sup>
Vapour pressure	8.13 kPa at 0°C; 21.28 kPa at 20°C
Stability	air- and light-sensitive; breaks down to phosgene, hydrogen chloride, and chlorine
Log octanol–water partition coefficient	1.97

### 1.3 *Organoleptic properties*

Chloroform has a characteristic odour and a burning, sweet taste. Its odour threshold values are 2.4 mg/litre in water and 420 mg/m<sup>3</sup> in air (Budvari et al., 1989; ATSDR, 1993).

### 1.4 *Major uses*

Commercial production of chloroform was 440 000 t in 1987. Chloroform has been used primarily in the production of chlorodifluoromethane, although smaller amounts have also been used as solvents, as cleaning agents, and in fumigants. Although chloroform was used in the past as an anaesthetic and in proprietary medicines, these applications have been prohibited in many countries.

### 1.5 *Environmental fate*

It is assumed that most chloroform present in water is ultimately transferred to air as a result of its volatility. Chloroform has a residence time in the atmosphere of several months and is removed from the atmosphere through chemical transformation. It is resistant to biodegradation by aerobic microbial populations of soils and aquifers subsisting on endogenous substrates or supplemented with acetate. Biodegradation may occur under anaerobic conditions. Bioconcentration in freshwater fish is low. Depuration is rapid (WHO, 1994a).

## 2. *ANALYTICAL METHODS*

There are several methods for the analysis of chloroform in air, water, and biological materials. The majority of these methods are based on direct column injection, adsorption on activated adsorbent or condensation in a cool trap, then desorption by solvent extraction or evaporation by heating and subsequent gas chromatographic analysis. In water, detection limits range from 0.02 to 1 µg/litre (WHO, 1994a; ISO, 1997).

### 3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

#### 3.1 Outdoor air

Chloroform levels in ambient air in remote areas of the USA range from 0.1 to 0.25  $\mu\text{g}/\text{m}^3$ . In urban and source-dominated areas, concentrations are 0.3–9.9  $\mu\text{g}/\text{m}^3$  and 4.1–110  $\mu\text{g}/\text{m}^3$ , respectively (ATSDR, 1993). The population-weighted mean concentration of chloroform at 17 urban sites sampled across Canada in 1989 was 0.2  $\mu\text{g}/\text{m}^3$  (Environment Canada, 1992).

Hourly average concentrations of chloroform in the Netherlands, determined during 1979–1981, were generally 0.15  $\mu\text{g}/\text{m}^3$  (estimated detection limit) or less, the maximum value being 10  $\mu\text{g}/\text{m}^3$  (den Hartog, 1980, 1981). Average concentrations of chloroform during 1990 in four German cities (Berlin, Tübingen, Freudenstadt, and Leipzig) ranged from 0.26 to 0.9  $\mu\text{g}/\text{m}^3$ ; the maximum value was 30  $\mu\text{g}/\text{m}^3$ , detected in Tübingen (Toxicology and Environmental Health Institute of Munich Technical University, 1992).

#### 3.2 Indoor air

Concentrations of chloroform in indoor air are generally higher than those in ambient outdoor air owing primarily to volatilization during water use. In a population survey in the USA, the observed increase was approximately 85%, which was consistent with assumptions concerning daily water use and likely release of chloroform from water into air (Wallace, 1987).

In a nationwide survey of 757 randomly selected one-family houses in Canada sampled over a 10-month period in 1991, the mean level of chloroform in indoor air was 4.1  $\mu\text{g}/\text{m}^3$ ; the maximum value was 69  $\mu\text{g}/\text{m}^3$  (Otson et al., 1992). Ullrich (1982) reported comparable concentrations in indoor air (1–3  $\mu\text{g}/\text{m}^3$ ) in Germany.

Chloroform levels in the air of enclosed swimming pools are also increased as a result of transfer from water. They vary as a function of several factors, such as the degree of ventilation, the level of chlorination, water temperature, the degree of mixing at the water surface, and the quantity of organic precursors present (Lahl et al., 1981a). Over a period of 11 months, the levels of chloroform directly above the water surface in indoor public swimming pools in Bremen, Germany, ranged from 10 to 380  $\mu\text{g}/\text{m}^3$ , with an average of about 100  $\mu\text{g}/\text{m}^3$  (Bätjer et al., 1980; Lahl et al., 1981a). Ullrich (1982) reported a similar mean value in four public swimming pools in Germany.

In an experimental study in which the mean concentration of chloroform in water in an indoor swimming pool was increased from 159 to 553  $\mu\text{g}/\text{litre}$ , corresponding mean air chloroform levels ranged from 2.9 to 8.0  $\text{mg}/\text{m}^3$  (Levesque et al., 1994).

#### 3.3 Water

Sources of chloroform in the aquatic environment include paper bleaching with chlorine, chlorination of recreational (pool) water, cooling water, and

wastewater. Chloroform is present in drinking-water through direct contamination of the source and through formation from naturally occurring organic compounds during chlorination. The rate and degree of formation of chloroform during chlorination are a function primarily of the concentrations of chlorine and humic acid, temperature, and pH. Levels vary seasonally, with concentrations generally being greater in summer than in winter (WHO, 1994a).

Concentrations of chloroform in groundwater vary widely, depending principally on proximity to hazardous waste sites (ATSDR, 1993). For example, chloroform was detected at levels ranging from 11 to 866 µg/litre in samples from five out of six monitoring wells drilled 64 m apart in a direction perpendicular to the northward flow of groundwater at a contaminated site in Pittman, Nevada, USA (the depth of unconfined groundwater was 2–4 m at this selected site) (Kerfoot, 1987).

Finished drinking-water collected in 1988–1989 from 35 US sources, 10 of which were located in California, in all four seasons contained median concentrations of chloroform ranging from 9.6 to 15 µg/litre. The overall median for all four seasons was 14 µg/litre (Krasner et al., 1989). In a 1987–1989 survey conducted in the USA, the mean chloroform concentration in finished water for surface water systems serving more than 10 000 people was 38.9 µg/litre (90th percentile, 74.4 µg/litre). The comparable mean value in the distribution system was 58.7 µg/litre (US EPA, 1992).

In a national survey of the water supplies of 70 communities in Canada conducted during the winter of 1976–1977, concentrations of chloroform in treated water of the distribution system 0.8 km from the treatment plant averaged 22.7 µg/litre (Williams et al., 1980). Concentrations at 10 different locations in southern Ontario sampled in the early 1980s were 4.5–60 µg/litre in water leaving the treatment plant and 7.1–63 µg/litre 1.6 km from the plant (Oliver, 1983). In a more recent survey of samples collected during winter and summer of 1993 at 53 sites in nine provinces of Canada, chloroform was the major THM detected at all but three sites, these being groundwater sources that were treated with minimal chlorination. The contribution of chloroform to total THMs (ranging from 75.5 to 91.4%) was higher in summer than in winter and was slightly higher for chlorine–chlorine versus chlorine–chloramine or ozone–chloramine treatment. Although the majority of treatment facilities had relatively low total THM levels (<50 µg/litre), a small number had relatively high levels (>100 µg/litre), particularly in the summer (except for chlorine–chloramine disinfection) (Health Canada, 1995).

Chloroform levels in drinking-water in 100 German cities sampled in 1977 ranged from <0.1 to 14.2 µg/litre and averaged 1.3 µg/litre. Concentrations were similar in other surveys conducted in Germany in the late 1970s and early 1980s (Lahl et al., 1981a).

Mean levels of chloroform in drinking-water in the Netherlands in 1994 ranged up to 8.9 µg/litre (Versteegh et al., 1996).

### **3.4 Food**

In an early study in Germany, chloroform was detected in several foodstuffs, in particular decaffeinated coffee (20 µg/kg), olive oil (28 µg/kg), pork (10 µg/kg),

and sausages (17 µg/kg). Occasionally, concentrations were higher: up to 80 µg/kg in coffee and 90 µg/kg in sausages. Levels of 1–10 µg/kg were detected in flour products, potatoes, cod liver oil, margarine, lard, fish, mussels, and milk; levels in most foodstuffs, however, were less than 1 µg/kg (Bauer, 1981).

Chloroform was detected in about 90 of 300 samples in a market basket survey of 231 "table-ready" foodstuffs (prepared and cooked as normally served) in the USA, most often in fat-containing samples (Daft, 1988). In a later account (Daft, 1989), it was reported that chloroform concentrations of 2–830 µg/kg of food were detected in 68% of 549 samples of foodstuffs obtained in a market basket survey (average of 71 µg/kg).

Chloroform was not detected in composite samples of meat/fish/poultry or in composite samples of oil/fat in 39 different foods in the USA, although it should be noted that the quantification limits were higher (18–28 µg/kg) than those in the studies described above. However, a chloroform concentration of 17 µg/litre was found in the composite of dairy foods (Entz et al., 1982).

Concentrations of chloroform in soft drinks range from 3 to 50 µg/litre, with levels for cola being at the upper end of the range (Abdel-Rahman, 1982; Entz et al., 1982; Wallace et al., 1984).

### 3.5 *Estimated total exposure and relative contribution of drinking-water*

Based on a daily inhalation volume for adults of 20 m<sup>3</sup>, a body weight of 60 kg, the assumption that 20 out of 24 hours are spent indoors, and the mean levels of chloroform in indoor air presented above (1–4 µg/m<sup>3</sup>), the mean intake of chloroform from indoor air for the general population is estimated to be 0.3–1.1 µg/kg of body weight per day.

Individuals may be exposed during showering to elevated concentrations of chloroform from chlorinated tap-water (Jo et al., 1990a,b). Based on experimental studies with humans, these authors concluded that the contribution of dermal exposure was approximately equivalent to inhalation exposure during showering and that the average intake of chloroform (inhalation and dermal absorption) was 0.5 µg/kg of body weight per shower for a person weighing 70 kg.

Based on a review of relevant estimates, Maxwell et al. (1991) concluded that the ratio of the dose of chloroform received over a lifetime from inhalation to that received from ingestion of drinking-water is probably in the range of 0.6–1.5 but could be as high as 5.7. The ratio of the dose received dermally compared with that received orally over a lifetime from drinking-water was considered to be approximately 0.3 but could be as high as 1.8.

Based on daily consumption of 2 litres of drinking-water for adults, a body weight of 60 kg, and the mean levels of chloroform presented above (generally <20 µg/litre), the estimated mean intake of chloroform from drinking-water for the general population is less than 0.7 µg/kg of body weight per day. Actual levels of exposure may be less than those estimated on the basis of mean levels in drinking-water, as most of the chloroform would be expelled from drinking-water that is heated before consumption (tea, coffee, soups, sauces). For example, approximately 96% of the total volatile halogenated hydrocarbon fraction was eliminated in water

boiling for 5 minutes, whereas 50–90% was eliminated upon heating at 70–90°C (Bauer, 1981). Owing to the wide variations in concentrations of chloroform in water supplies, intake from drinking-water could be considerably greater than estimated here for some segments of the general population.

Based on a daily ingestion of solid foodstuffs for adults of 1.5 kg (WHO, 1994b), a mean body weight of 60 kg, and the mean level and percent detection of chloroform in foodstuffs in the market basket survey reported by Daft (1989), the estimated intake of chloroform from foodstuffs is approximately 1 µg/kg of body weight per day.

Based on estimates of mean exposure from various media, therefore, the general population is exposed to chloroform principally in food, drinking-water, and indoor air, in approximately equivalent amounts. The estimated intake from outdoor air is considerably less. The total estimated mean intake is approximately 2–3 µg/kg of body weight per day. For some individuals living in dwellings supplied with tap-water containing relatively high concentrations of chloroform, estimated total intakes from drinking-water through ingestion, inhalation, and dermal contact are up to 10 µg/kg of body weight per day.

Pools are also an important source of exposure to chloroform for swimmers. Based on an experimentally determined relationship, Levesque et al. (1994) estimated that the daily dose of chloroform resulting from a 1-hour swim (65 µg/kg of body weight per day) in conditions commonly found in public swimming pools is 141 times greater than that for a 10-minute shower and 93 times greater than that for tap-water ingestion.

#### **4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS**

The kinetics and metabolism of chloroform were reviewed in WHO (1994a). Chloroform is well absorbed in animals and humans after oral administration, but the absorption kinetics are dependent upon the vehicle of delivery. After inhalation exposure in humans, 60–80% of the inhaled quantity is absorbed, with kinetics being dependent upon concentration and species-specific metabolic capacities. Chloroform is readily absorbed through the skin of humans and animals, and significant dermal absorption of chloroform from water while showering has been demonstrated (Jo et al., 1990a). Hydration of the skin appears to accelerate absorption of chloroform.

Chloroform distributes throughout the whole body, with levels being highest in the fat, blood, liver, kidneys, lungs, and nervous system. Distribution is dependent on exposure route; extrahepatic tissues receive a higher dose from inhaled or dermally absorbed chloroform than from ingested chloroform. Placental transfer of chloroform has been demonstrated in several animal species and humans. Unmetabolized chloroform is retained longer in fat than in any other tissue.

The oxidative biotransformation of chloroform is catalysed by cytochrome P-450 to produce trichloromethanol. Loss of hydrogen chloride from trichloromethanol produces phosgene as a reactive intermediate. Phosgene may be detoxified by reaction with water to produce carbon dioxide or with thiols, including glutathione and cysteine, to produce adducts. The reaction of phosgene with tissue

proteins is associated with cell damage and death. Little binding of chloroform metabolites to DNA is observed. Chloroform also undergoes cytochrome P-450 catalysed reductive biotransformation to produce the dichloromethyl radical, which becomes covalently bound to tissue lipids. A role for reductive biotransformation in the cytotoxicity of chloroform has not been established.

In animals and humans exposed to chloroform, carbon dioxide and unchanged chloroform are eliminated in the expired air. The fraction of the dose eliminated as carbon dioxide varies with the dose and the species. The rate of biotransformation to carbon dioxide is higher in rodent (hamster, mouse, rat) hepatic and renal microsomes than in human hepatic and renal microsomes. Also, chloroform is biotransformed more rapidly in mouse than in rat renal microsomes.

## 5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

### 5.1 Acute exposure

The liver is the target organ for acute toxicity in rats and several strains of mice. Liver damage is characterized mainly by early fatty infiltration and balloon cells, progressing to centrilobular necrosis and then massive necrosis. The kidney is the target organ in male mice of other more sensitive strains. The kidney damage starts with hydropic degeneration and progresses to necrosis of the proximal tubules. Significant renal toxicity has not been observed in female mice of any strain.

Acute toxicity varies depending upon the strain, sex, and vehicle. In mice, the oral LD<sub>50</sub> values range from 36 to 1366 mg/kg of body weight; for rats, they range from 450 to 2000 mg/kg of body weight (WHO, 1994a).

### 5.2 Short-term exposure

The most universally observed toxic effects of chloroform are liver and kidney damage. The severity of these effects per unit dose administered depends on the species, vehicle, and method by which the chloroform is administered.

Many histological and biochemical parameters were examined in female and male CD1 mice (7–12 per sex per group) administered chloroform at 0, 50, 125, or 250 mg/kg of body weight per day in water by gavage for 14 and 90 days (Munson et al., 1982). After 90 days, a depression in the number of antibody-forming cells was found at the highest dose level in both sexes. In females at the highest dose level, a decrease in cell-mediated-type hypersensitivity was observed. Liver weight was increased after 90 days of exposure at all dose levels in females and at the highest dose level in males. After 90 days of exposure, the animals demonstrated tolerance against a challenging dose of 1000 mg/kg of body weight. Histological changes observed in the kidneys of all dosed animals included small intertubular collections of chronic inflammatory cells; in the liver, they included generalized hydropic degeneration of hepatocytes and occasional small focal collections of lymphocytes. In females, small amounts of extravasated bile were occasionally noted in the sinusoidal Kupffer cells.

Jorgenson & Rushbrook (1980) administered chloroform to female B6C3F<sub>1</sub> mice for 90 days at concentrations of 0, 200, 400, 600, 900, 1800, or 2700 mg/litre of drinking-water (equal to 0, 34, 66, 92, 132, 263, and 400 mg/kg of body weight). In the first week of the experiment, some mice in the highest dose group died of dehydration as a result of reduced water consumption. Concentration-related depression of the central nervous system occurred. The only treatment-related histopathological findings consisted of a mild adaptive and transitory fatty change in the livers of animals dosed with 66 mg/kg of body weight per day or more and a mild lymphoid atrophy of the spleen at 92 mg/kg of body weight per day and higher dose levels.

There is evidence that the vehicle in which chloroform is administered significantly affects its toxicity. Bull et al. (1986) reported that chloroform administered by gavage in corn oil was significantly more hepatotoxic than equivalent doses administered in an aqueous emulsion (2% Emulphor, polyoxyethylated vegetable oil, GAF Corp.) to male and female B6C3F<sub>1</sub> mice (10 per sex per group) administered doses of 0, 60, 130, or 270 mg/kg of body weight per day for 90 days, based on examination of serum hepatic enzymes and hepatic histopathology.

In female B6C3F<sub>1</sub> mice exposed for 1 week to chloroform vapour at concentrations of 0, 4.9, 14.7, 49, 147, 490, or 1470 mg/m<sup>3</sup>, there was increased cell proliferation in the nasal passages. This response was markedly less than that in F344 rats exposed to similar concentrations (Mery et al., 1994).

Palmer et al. (1979) exposed 10 male and 10 female SPF Sprague-Dawley rats to chloroform by intragastric gavage (in toothpaste) daily for 13 weeks. Dose levels were 0, 15, 30, 150, or 410 mg/kg of body weight per day. At 150 mg/kg of body weight per day, there was "distinct influence on relative liver and kidney weight" (significance not specified). At the highest dose, there was increased liver weight with fatty change and necrosis, gonadal atrophy in both sexes, and increased cellular proliferation in bone marrow.

In a 90-day study by Chu et al. (1982), groups of 20 male and 20 female Sprague-Dawley rats were exposed to chloroform via drinking-water at dose levels of 0, 0.17, 1.3, 12, or 40 mg/day for males and 0, 0.12, 1.3, 9.5, or 29 mg/day for females; this was followed by 90 days of recovery. Water and food intake were reduced in the highest dose group. At the 40 mg/day level, mortality was increased. Upon histological examination, there were mild liver and thyroid lesions, especially in the highest dose group. In livers of both males and females, there was an increase in cytoplasmic homogeneity, density of the hepatocytes in the periportal area, mid-zonal and centrilobular increase in cytoplasmic volume, vacuolation due to fatty infiltration, and occasional nucleic vesiculation and hyperplasia of biliary epithelial cells. Thyroid lesions consisted of a reduction in follicular size and colloid density, increase in epithelial cell height, and occasional collapse of follicles. Liver and thyroid lesions diminished in severity during the 90-day recovery period.

Jorgenson & Rushbrook (1980) administered chloroform in drinking-water to male Osborne-Mendel rats for 90 days at concentrations of 0, 200, 400, 600, 900, or 1800 mg/litre (equal to 0, 20, 38, 57, 81, and 160 mg/kg of body weight per day). A concentration-related central nervous system depression was seen. Body weights in

There have also been a smaller number of epidemiological investigations of associations between consumption of chlorinated drinking-water and developmental/reproductive effects. In a recent review of relevant information, Reif et al. (1996) concluded that the existing database was inadequate to determine an association between exposure to disinfection by-products and adverse reproductive and developmental effects, drawing attention particularly to the variability in exposure assessments and examined end-points and potential for exposure misclassification and confounding.

## 7. GUIDELINE VALUE

The weight of evidence for genotoxicity is considered negative (WHO, 1994a). The weight of evidence for liver tumours in mice is consistent with a threshold mechanism of induction. Although it is plausible that kidney tumours in rats may similarly be associated with a threshold mechanism, there are some limitations of the database in this regard.

A guideline value can therefore be developed on the basis of a TDI for threshold effects. The most universally observed toxic effect of chloroform is damage to the centrilobular region of the liver. The severity of these effects per unit dose administered depends on the species, vehicle, and method by which the chloroform is administered. The lowest dose at which liver damage has been observed is 15 mg/kg of body weight per day administered to beagle dogs in a toothpaste base over a period of 7.5 years. Effects at lower doses were not examined. Somewhat higher doses are required to produce hepatotoxic effects in other species. Effects in the proximal tubules of the kidney cortex have been observed in male mice of sensitive strains and in both male and female rats of several strains. Levels inducing adverse histopathological effects in the range of 30 mg/kg of body weight per day have been reported in some studies in sensitive strains.

Based on the study by Heywood et al. (1979) in which slight hepatotoxicity (increases in hepatic serum enzymes and fatty cysts) was observed in beagle dogs ingesting 15 mg/kg of body weight per day in toothpaste for 7.5 years, and incorporating an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for use of a LOAEL rather than a NOAEL and a subchronic study), a TDI of 13 µg per kg of body weight per day (corrected for 6 days/week dosing) is derived. Allocation of 50% of total intake to drinking-water is a reasonable default based on estimates of mean exposure that indicate that the general population is exposed to chloroform principally in food, drinking-water, and indoor air in approximately equivalent amounts and that most of the chloroform in indoor air is present as a result of volatilization from drinking-water. Moreover, the population is additionally exposed dermally to chloroform in drinking-water during showering. Based on an average body weight of 60 kg and daily ingestion of 2 litres of drinking-water, the guideline value is 200 µg/litre (rounded figure).

It is noted that a drinking-water concentration for a  $10^{-5}$  excess lifetime cancer risk estimated on the basis of the default linearized multistage model for renal tumours in rats is similar to the value developed on the basis of non-neoplastic effects.

It is cautioned that where local circumstances require that a choice be made between meeting microbiological guidelines or guidelines for disinfection by-products such as chloroform, the microbiological quality must always take precedence. Efficient disinfection must *never* be compromised.

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## Annex 1

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## Annex 2

### Tables of guideline values

The following tables present a summary of guideline values for 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.

#### *Notes to tables*

<sup>a</sup> (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.

<sup>b</sup> 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.

Table 1. Chemicals of health significance in drinking-water

## A. Inorganic constituents

	Guideline value (mg/litre)	Remarks
boron	0.5 (P) <sup>a</sup>	
copper	2 (P)	Based on acute gastrointestinal effects
nickel	0.02 (P)	
nitrate (as NO <sub>3</sub> <sup>-</sup> )	50 (acute)	The sum of the ratio of the concentration of each to its respective (acute) guideline value should not exceed 1
nitrite (as NO <sub>2</sub> <sup>-</sup> )	3 (acute) 0.2 (P) (chronic)	
uranium	0.002 (P)	

## B. Organic constituents

	Guideline value (µg/litre)	Remarks
benzo[ <i>a</i> ]pyrene	0.7 <sup>b</sup>	For excess risk of 10 <sup>-5</sup>
edetic acid (EDTA)	600	Applies to the free acid
microcystin-LR	1 (P)	Applies to total microcystin-LR (free plus cell-bound)

**C. Pesticides**

	<b>Guideline value (µg/litre)</b>	<b>Remarks</b>
bentazone	300	
carbofuran	7	
cyanazine	0.6	
1,2-dibromoethane	0.4–15 <sup>b</sup> (P)	For excess risk of 10 <sup>-5</sup>
2,4-dichlorophenoxyacetic acid (2,4-D)	30	
1,2-dichloropropane (1,2-DCP)	40 (P)	
diquat	10 (P)	
pentachlorophenol	9 <sup>b</sup> (P)	For excess risk of 10 <sup>-5</sup>
terbuthylazine (TBA)	7	

**D. Disinfectant by-product**

	<b>Guideline value (µg/litre)</b>	<b>Remarks</b>
chloroform	200	

*Table 2. Chemicals not of health significance at concentrations normally found in drinking-water*

<b>Chemical</b>	<b>Remarks</b>
fluoranthene	U
glyphosate	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.

