

12

Chemical fact sheets

The background documents referred to in this chapter may be found on the Water Sanitation and Health website at http://www.who.int/water_sanitation_health/dwq/guidelines/en/.

12.1 Acrylamide

Residual acrylamide monomer occurs in polyacrylamide coagulants used in the treatment of drinking-water. In general, the maximum authorized dose of polymer is 1 mg/litre. At a monomer content of 0.05%, this corresponds to a maximum theoretical concentration of 0.5 µg/litre of the monomer in water. Practical concentrations may be lower by a factor of 2–3. This applies to the anionic and non-ionic polyacrylamides, but residual levels from cationic polyacrylamides may be higher. Polyacrylamides are also used as grouting agents in the construction of drinking-water reservoirs and wells. Additional human exposure might result from food, owing to the use of polyacrylamide in food processing and the potential formation of acrylamide in foods cooked at high temperatures.

Guideline value	0.0005 mg/litre (0.5 µg/litre)
Occurrence	Concentrations of a few micrograms per litre have been detected in tap water.
Basis of guideline derivation	Combined mammary, thyroid and uterine tumours observed in female rats in a drinking-water study, and using the linearized multistage model
Limit of detection	0.032 µg/litre by GC; 0.2 µg/litre by HPLC; 10 µg/litre by HPLC with UV detection
Treatment achievability	Conventional treatment processes do not remove acrylamide. Acrylamide concentrations in drinking-water are controlled by limiting either the acrylamide content of polyacrylamide flocculants or the dose used, or both.
Additional comments	Although the practical quantification level for acrylamide in most laboratories is above the guideline value (generally in the order of 1 µg/litre), concentrations in drinking-water can be controlled by product and dose specification.

Toxicological review

Following ingestion, acrylamide is readily absorbed from the gastrointestinal tract and widely distributed in body fluids. Acrylamide can cross the placenta. It is neurotoxic, affects germ cells and impairs reproductive function. In mutagenicity assays, acrylamide was negative in the Ames test but induced gene mutations in mammalian cells and chromosomal aberrations *in vitro* and *in vivo*. In a long-term carcinogenicity study in rats exposed via drinking-water, acrylamide induced scrotal, thyroid and adrenal tumours in males and mammary, thyroid and uterine tumours in females. IARC has placed acrylamide in Group 2A. Recent data have shown that exposure to acrylamide from cooked food is much higher than previously thought. The significance of this new information for the risk assessment has not yet been determined.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to acrylamide. The 1993 Guidelines established a guideline value of 0.0005 mg/litre associated with an upper-bound excess lifetime cancer risk of 10^{-5} , noting that although the practical quantification level for acrylamide is generally in the order of 0.001 mg/litre, concentrations in drinking-water can be controlled by product and dose specification.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Acrylamide in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/71).

12.2 Alachlor

Alachlor (CAS No. 15972-60-8) is a pre- and post-emergence herbicide used to control annual grasses and many broad-leaved weeds in maize and a number of other crops. It is lost from soil mainly through volatilization, photodegradation and biodegradation. Many alachlor degradation products have been identified in soil.

Guideline value	0.02 mg/litre
Occurrence	Has been detected in groundwater and surface water; has also been detected in drinking-water at levels below 0.002 mg/litre
Basis of guideline derivation	Calculated by applying the linearized multistage model to data on the incidence of nasal tumours in rats
Limit of detection	0.1 µg/litre by gas-liquid chromatography with electrolytic conductivity detection in the nitrogen mode or by capillary column GC with a nitrogen-phosphorus detector
Treatment achievability	0.001 mg/litre should be achievable using GAC

Toxicological review

On the basis of available experimental data, evidence for the genotoxicity of alachlor is considered to be equivocal. However, a metabolite of alachlor, 2,6-diethylaniline, has been shown to be mutagenic. Available data from two studies in rats clearly indicate that alachlor is carcinogenic, causing benign and malignant tumours of the nasal turbinate, malignant stomach tumours and benign thyroid tumours.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to alachlor, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Alachlor was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines calculated a guideline value of 0.02 mg/litre for alachlor in drinking-water, corresponding to an upper-bound excess lifetime cancer risk of 10^{-5} .

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Alachlor in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/31).

12.3 Aldicarb

Aldicarb (CAS No. 116-06-3) is a systemic pesticide used to control nematodes in soil and insects and mites on a variety of crops. It is very soluble in water and highly mobile in soil. It degrades mainly by biodegradation and hydrolysis, persisting for weeks to months.

12. CHEMICAL FACT SHEETS

Guideline value	0.01 mg/litre
Occurrence	Frequently found as a contaminant in groundwater, particularly when associated with sandy soil; concentrations in well water as high as 500 µg/litre have been measured. Aldicarb sulfoxide and aldicarb sulfone residues are found in an approximately 1 : 1 ratio in groundwater.
ADI	0.003 mg/kg of body weight based on cholinesterase depression in a single oral dose study in human volunteers
Limit of detection	0.001 mg/litre by reverse-phase HPLC with fluorescence detection
Treatment achievability	0.001 mg/litre should be achievable using GAC or ozonation
Guideline derivation	
● allocation to water	10% of ADI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	The guideline value derived from the 1992 JMPR assessment was very similar to the guideline value derived in the second edition, which was therefore retained.

Toxicological review

Aldicarb is one of the most acutely toxic pesticides in use, although the only consistently observed toxic effect with both long-term and single-dose administration is acetylcholinesterase inhibition. It is metabolized to the sulfoxide and sulfone. Aldicarb sulfoxide is a more potent inhibitor of acetylcholinesterase than aldicarb itself, while aldicarb sulfone is considerably less toxic than either aldicarb or the sulfoxide. The weight of evidence indicates that aldicarb, aldicarb sulfoxide and aldicarb sulfone are not genotoxic or carcinogenic. IARC has concluded that aldicarb is not classifiable as to its carcinogenicity (Group 3).

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to aldicarb, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Aldicarb was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but a health-based guideline value of 0.01 mg/litre was derived for aldicarb in the 1993 Guidelines.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (1993) *Pesticide residues in food – 1992*. Rome, Food and Agriculture Organization of the United Nations, Joint FAO/WHO Meeting on Pesticide Residues (Report No. 116).

WHO (2003) *Aldicarb in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/72).

12.4 Aldrin and dieldrin

Aldrin (CAS No. 309-00-2) and dieldrin (CAS No. 60-57-1) are chlorinated pesticides that are used against soil-dwelling pests, for wood protection and, in the case of dieldrin, against insects of public health importance. Since the early 1970s, a number of countries have either severely restricted or banned the use of both compounds, particularly in agriculture. The two compounds are closely related with respect to their toxicology and mode of action. Aldrin is rapidly converted to dieldrin under most environmental conditions and in the body. Dieldrin is a highly persistent organochlorine compound that has low mobility in soil, can be lost to the atmosphere and bioaccumulates. Dietary exposure to aldrin/dieldrin is very low and decreasing.

Guideline value	0.00003 mg/litre (0.03 µg/litre) combined aldrin and dieldrin
Occurrence	Concentrations of aldrin and dieldrin in drinking-water normally less than 0.01 µg/litre; rarely present in groundwater
PTDI	0.1 µg/kg of body weight (combined total for aldrin and dieldrin), based on NOAELs of 1 mg/kg of diet in the dog and 0.5 mg/kg of diet in the rat, which are equivalent to 0.025 mg/kg of body weight per day in both species, and applying an uncertainty factor of 250 based on concern about carcinogenicity observed in mice
Limit of detection	0.003 µg/litre for aldrin and 0.002 µg/litre for dieldrin by GC with ECD
Treatment achievability	0.02 µg/litre should be achievable using coagulation, GAC or ozonation
Guideline derivation	
● allocation to water	1% of PTDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	Aldrin and dieldrin are listed under the Stockholm Convention on Persistent Organic Pollutants. Hence, monitoring may occur in addition to that required by drinking-water guidelines.

Toxicological review

Both compounds are highly toxic in experimental animals, and cases of poisoning in humans have occurred. Aldrin and dieldrin have more than one mechanism of toxicity. The target organs are the central nervous system and the liver. In long-term studies, dieldrin was shown to produce liver tumours in both sexes of two strains of

mice. It did not produce an increase in tumours in rats and does not appear to be genotoxic. IARC has classified aldrin and dieldrin in Group 3. It is considered that all the available information on aldrin and dieldrin taken together, including studies on humans, supports the view that, for practical purposes, these chemicals make very little contribution, if any, to the incidence of cancer in humans.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to aldrin and dieldrin, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.03 µg/litre was recommended for aldrin and dieldrin, based on the ADI recommended by JMPR in 1970 for aldrin and dieldrin residues separately or together and reaffirmed by toxicological data available in 1977. The 1993 Guidelines confirmed the health-based guideline value of 0.03 µg/litre for aldrin and dieldrin, based on the reaffirmation of the ADI recommended in 1977 by JMPR.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (1995) *Pesticide residues in food – 1994. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment Groups*. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper 127).

WHO (2003) *Aldrin and dieldrin in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/73).

12.5 Aluminium

Aluminium is the most abundant metallic element and constitutes about 8% of the Earth's crust. Aluminium salts are widely used in water treatment as coagulants to reduce organic matter, colour, turbidity and microorganism levels. Such use may lead to increased concentrations of aluminium in finished water. Where residual concentrations are high, undesirable colour and turbidity may ensue. Concentrations of aluminium at which such problems may occur are highly dependent on a number of water quality parameters and operational factors at the water treatment plant. Aluminium intake from foods, particularly those containing aluminium compounds used as food additives, represents the major route of aluminium exposure for the general

public. The contribution of drinking-water to the total oral exposure to aluminium is usually less than 5% of the total intake.

In humans, aluminium and its compounds appear to be poorly absorbed, although the rate and extent of absorption have not been adequately studied for all sectors of the population. The degree of aluminium absorption depends on a number of parameters, such as the aluminium salt administered, pH (for aluminium speciation and solubility), bioavailability and dietary factors. These parameters should be taken into consideration during tissue dosimetry and response assessment. The use of currently available animal studies to develop a guideline value for aluminium is not appropriate because of these specific toxicokinetic/toxicodynamic considerations.

There is little indication that orally ingested aluminium is acutely toxic to humans despite the widespread occurrence of the element in foods, drinking-water and many antacid preparations. It has been hypothesized that aluminium exposure is a risk factor for the development or acceleration of onset of Alzheimer disease (AD) in humans. The 1997 WHO EHC document for aluminium concludes that:

On the whole, the positive relationship between aluminium in drinking-water and AD, which was demonstrated in several epidemiological studies, cannot be totally dismissed. However, strong reservations about inferring a causal relationship are warranted in view of the failure of these studies to account for demonstrated confounding factors and for total aluminium intake from all sources.

Taken together, the relative risks for AD from exposure to aluminium in drinking-water above 100 µg/litre, as determined in these studies, are low (less than 2.0). But, because the risk estimates are imprecise for a variety of methodological reasons, a population-attributable risk cannot be calculated with precision. Such imprecise predictions may, however, be useful in making decisions about the need to control exposures to aluminium in the general population.

Owing to the limitations of the animal data as a model for humans and the uncertainty surrounding the human data, a health-based guideline value for aluminium cannot be derived at this time.

The beneficial effects of the use of aluminium as a coagulant in water treatment are recognized. Taking this into account, and considering the health concerns about aluminium (i.e., its potential neurotoxicity), a practicable level is derived, based on optimization of the coagulation process in drinking-water plants using aluminium-based coagulants, to minimize aluminium levels in finished water.

Several approaches are available for minimizing residual aluminium concentrations in treated water. These include use of optimum pH in the coagulation process, avoiding excessive aluminium dosage, good mixing at the point of application of the coagulant, optimum paddle speeds for flocculation and efficient filtration of the aluminium floc. Under good operating conditions, concentrations of aluminium of 0.1 mg/litre or less are achievable in large water treatment facilities. Small facilities (e.g., those serving fewer than 10 000 people) might experience some difficulties in attaining this level, because the small size of the plant provides little buffering for fluctuation in operation; moreover, such facilities often have limited resources and limited

access to the expertise needed to solve specific operational problems. For these small facilities, 0.2 mg/litre or less is a practicable level for aluminium in finished water.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to aluminium. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 0.2 mg/litre was established for aluminium, based on aesthetic considerations (as a compromise between the use of aluminium compounds in water treatment and discoloration that may be observed if levels above 0.1 mg/litre remain in the distributed water). No health-based guideline value was recommended in the 1993 Guidelines, but the Guidelines confirmed that a concentration of 0.2 mg/litre in drinking-water provides a compromise between the practical use of aluminium salts in water treatment and discoloration of distributed water. No health-based guideline value was derived for aluminium in the addendum to the Guidelines published in 1998, owing to the limitations of the animal data as a model for humans and the uncertainty surrounding the human data. However, taking the beneficial effects of the use of aluminium as a coagulant in water treatment into account and considering the health concerns about aluminium (i.e., its potential neurotoxicity), a practicable level was derived based on optimization of the coagulation process in drinking-water plants using aluminium-based coagulants, to minimize aluminium levels in finished water. Under good operating conditions, concentrations of aluminium of 0.1 mg/litre or less are achievable in large water treatment facilities. For small facilities, 0.2 mg/litre or less is a practicable level for aluminium in finished water.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Aluminium in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/53).

12.6 Ammonia

The term ammonia includes the non-ionized (NH_3) and ionized (NH_4^+) species. Ammonia in the environment originates from metabolic, agricultural and industrial processes and from disinfection with chloramine. Natural levels in groundwater and surface water are usually below 0.2 mg/litre. Anaerobic groundwaters may contain up to 3 mg/litre. Intensive rearing of farm animals can give rise to much higher levels in surface water. Ammonia contamination can also arise from cement mortar pipe

linings. Ammonia in water is an indicator of possible bacterial, sewage and animal waste pollution.

Ammonia is a major component of the metabolism of mammals. Exposure from environmental sources is insignificant in comparison with endogenous synthesis of ammonia. Toxicological effects are observed only at exposures above about 200 mg/kg of body weight.

Ammonia in drinking-water is not of immediate health relevance, and therefore no health-based guideline value is proposed. However, ammonia can compromise disinfection efficiency, result in nitrite formation in distribution systems, cause the failure of filters for the removal of manganese and cause taste and odour problems (see also chapter 10).

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to ammonia. In the 1993 Guidelines, no health-based guideline value was recommended, but the Guidelines stated that ammonia could cause taste and odour problems at concentrations above 35 and 1.5 mg/litre, respectively.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Ammonia in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/1).

12.7 Antimony

Elemental antimony forms very hard alloys with copper, lead and tin. Antimony compounds have various therapeutic uses. Antimony was considered as a possible replacement for lead in solders, but there is no evidence of any significant contribution to drinking-water concentrations from this source. Daily oral uptake of antimony appears to be significantly higher than exposure by inhalation, although total exposure from environmental sources, food and drinking-water is very low compared with occupational exposure.

12. CHEMICAL FACT SHEETS

Guideline value	0.02 mg/litre
Occurrence	Concentrations in groundwater and surface water normally range from 0.1 to 0.2 µg/litre; concentrations in drinking-water appear to be less than 5 µg/litre.
TDI	6 µg/kg of body weight, based on a NOAEL of 6.0 mg/kg of body weight per day for decreased body weight gain and reduced food and water intake in a 90-day study in which rats were administered potassium antimony tartrate in drinking-water, using an uncertainty factor of 1000 (100 for inter- and intraspecies variation, 10 for the short duration of the study)
Limit of detection	0.01 µg/litre by EAAS; 0.1–1 µg/litre by ICP/MS; 0.8 µg/litre by graphite furnace atomic absorption spectrophotometry; 5 µg/litre by hydride generation AAS
Treatment achievability	Conventional treatment processes do not remove antimony. However, antimony is not normally a raw water contaminant. As the most common source of antimony in drinking-water appears to be dissolution from metal plumbing and fittings, control of antimony from such sources would be by product control.
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

There has been a significant increase in the toxicity data available since the previous review, although much of it pertains to the intraperitoneal route of exposure. The form of antimony in drinking-water is a key determinant of the toxicity, and it would appear that antimony leached from antimony-containing materials would be in the form of the antimony(V) oxo-anion, which is the less toxic form. The subchronic toxicity of antimony trioxide is lower than that of potassium antimony tartrate, which is the most soluble form. Antimony trioxide, due to its low bioavailability, is genotoxic only in some *in vitro* tests, but not *in vivo*, whereas soluble antimony(III) salts exert genotoxic effects *in vitro* and *in vivo*. Animal experiments from which the carcinogenic potential of soluble or insoluble antimony compounds may be quantified are not available. IARC has concluded that antimony trioxide is possibly carcinogenic to humans (Group 2B) on the basis of an inhalation study in rats, but that antimony trisulfide was not classifiable as to its carcinogenicity to humans (Group 3). However, chronic oral uptake of potassium antimony tartrate may not be associated with an additional carcinogenic risk, since antimony after inhalation exposure was carcinogenic only in the lung but not in other organs and is known to cause direct lung damage following chronic inhalation as a consequence of overload with insoluble particulates. Although there is some evidence for the carcinogenicity of certain antimony compounds by inhalation, there are no data to indicate carcinogenicity by the oral route.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to antimony. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was concluded that no action was required for antimony. A provisional guideline value for antimony was set at a practical quantification level of 0.005 mg/litre in the 1993 Guidelines, based on available toxicological data.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Antimony in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/74).

12.8 Arsenic¹

Arsenic is found widely in the earth's crust in oxidation states of -3, 0, +3 and +5, often as sulfides or metal arsenides or arsenates. In water, it is mostly present as arsenate (+5), but in anaerobic conditions, it is likely to be present as arsenite (+3). It is usually present in natural waters at concentrations of less than 1–2 µg/litre. However, in waters, particularly groundwaters, where there are sulfide mineral deposits and sedimentary deposits deriving from volcanic rocks, the concentrations can be significantly elevated.

Arsenic is found in the diet, particularly in fish and shellfish, in which it is found mainly in the less toxic organic form. There are only limited data on the proportion of inorganic arsenic in food, but these indicate that approximately 25% is present in the inorganic form, depending on the type of food. Apart from occupational exposure, the most important routes of exposure are through food and drinking-water, including beverages that are made from drinking-water. Where the concentration of arsenic in drinking-water is 10 µg/litre or greater, this will be the dominant source of intake. In circumstances where soups or similar dishes are a staple part of the diet, the drinking-water contribution through preparation of food will be even greater.

Provisional guideline value	0.01 mg/litre The guideline value is designated as provisional in view of the scientific uncertainties.
Occurrence	Levels in natural waters generally range between 1 and 2 µg/litre, although concentrations may be elevated (up to 12 mg/litre) in areas containing natural sources.

¹ As arsenic is one of the chemicals of greatest health concern in some natural waters, its chemical fact sheet has been expanded.

Basis of guideline derivation	There remains considerable uncertainty over the actual risks at low concentrations, and available data on mode of action do not provide a biological basis for using either linear or non-linear extrapolation. In view of the significant uncertainties surrounding the risk assessment for arsenic carcinogenicity, the practical quantification limit in the region of 1–10 µg/litre and the practical difficulties in removing arsenic from drinking-water, the guideline value of 10 µg/litre is retained. In view of the scientific uncertainties, the guideline value is designated as provisional.
Limit of detection	0.1 µg/litre by ICP/MS; 2 µg/litre by hydride generation AAS or FAAS
Treatment achievability	It is technically feasible to achieve arsenic concentrations of 5 µg/litre or lower using any of several possible treatment methods. However, this requires careful process optimization and control, and a more reasonable expectation is that 10 µg/litre should be achievable by conventional treatment, e.g., coagulation.
Additional comments	<ul style="list-style-type: none"> • A management guidance document on arsenic is in preparation. • The guideline value is supported by the JECFA PTWI of 15 µg/kg of body weight, if a 20% allocation to drinking-water is assumed. • In many countries, this guideline value may not be attainable. Where this is the case, every effort should be made to keep concentrations as low as possible.

Toxicological review

Both pentavalent and trivalent soluble arsenic compounds are rapidly and extensively absorbed from the gastrointestinal tract. Metabolism is characterized by 1) reduction of pentavalent to trivalent arsenic and 2) oxidative methylation of trivalent arsenic to form mono-, di- and trimethylated products. Methylation of inorganic arsenic facilitates the excretion of inorganic arsenic from the body, as the end-products monomethylarsonic acid and dimethylarsinic acid are readily excreted in urine. There are major qualitative and quantitative interspecies differences in methylation, but in humans and most common laboratory animals, inorganic arsenic is extensively methylated, and the metabolites are excreted primarily in the urine. There is large interindividual variation in arsenic methylation in humans, probably due to a wide difference in the activity of methyltransferases and possible polymorphism. Ingested organoarsenicals are much less extensively metabolized and more rapidly eliminated in urine than inorganic arsenic.

Arsenic has not been demonstrated to be essential in humans. The acute toxicity of arsenic compounds in humans is predominantly a function of their rate of removal from the body. Arsine is considered to be the most toxic form, followed by the arsenites, the arsenates and organic arsenic compounds. Acute arsenic intoxication associated with the ingestion of well water containing very high concentrations (21.0 mg/litre) of arsenic has been reported.

Signs of chronic arsenicism, including dermal lesions such as hyper- and hypopigmentation, peripheral neuropathy, skin cancer, bladder and lung cancers and

peripheral vascular disease, have been observed in populations ingesting arsenic-contaminated drinking-water. Dermal lesions were the most commonly observed symptom, occurring after minimum exposure periods of approximately 5 years. Effects on the cardiovascular system were observed in children consuming arsenic-contaminated water (mean concentration 0.6 mg/litre) for an average of 7 years.

Numerous epidemiological studies have examined the risk of cancers associated with arsenic ingestion through drinking-water. Many are ecological-type studies, and many suffer from methodological flaws, particularly in the measurement of exposure. However, there is overwhelming evidence that consumption of elevated levels of arsenic through drinking-water is causally related to the development of cancer at several sites. Nevertheless, there remain considerable uncertainty and controversy over both the mechanism of carcinogenicity and the shape of the dose–response curve at low intakes. IPCS (2001) concluded that long-term exposure to arsenic in drinking-water is causally related to increased risks of cancer in the skin, lungs, bladder and kidney, as well as other skin changes, such as hyperkeratosis and pigmentation changes. These effects have been demonstrated in many studies using different study designs. Exposure–response relationships and high risks have been observed for each of these end-points. The effects have been most thoroughly studied in Taiwan, China, but there is considerable evidence from studies on populations in other countries as well. Increased risks of lung and bladder cancer and of arsenic-associated skin lesions have been reported to be associated with ingestion of drinking-water at concentrations of ≤ 50 μg of arsenic per litre. There is a need for more analytical epidemiological studies to determine the dose–time response for skin lesions, as well as cancer, in order to assist in developing suitable interventions and determining practical intervention policies.

Inorganic arsenic compounds are classified by IARC (1987) in Group 1 (carcinogenic to humans) on the basis of sufficient evidence for carcinogenicity in humans and limited evidence for carcinogenicity in animals. Although there is a substantial database on the association between both internal and skin cancers and the consumption of arsenic in drinking-water, there remains considerable uncertainty over the actual risks at low concentrations. USNRC (2001), in its updated evaluation, concluded that “the available mode-of-action data on arsenic do not provide a biological basis for using either a linear or nonlinear extrapolation.” The maximum likelihood estimates, using a linear extrapolation, for bladder and lung cancer for populations in the United States exposed to 10 μg of arsenic per litre in drinking-water are, respectively, 12 and 18 per 10 000 population for females and 23 and 14 per 10 000 population for males. The actual numbers indicated by these estimated risks would be very difficult to detect by current epidemiological methods. There is also uncertainty over the contribution of arsenic in food – a higher intake of inorganic arsenic from food would lead to a lower risk estimate for water – and the impact of factors such as variation in the metabolism of arsenic and nutritional status. Some studies in areas with arsenic concentrations somewhat above 50 μg /litre have not detected arsenic-related

adverse effects in the residents. It remains possible that the estimates of cancer risk associated with various arsenic intakes are overestimates. The concentration of arsenic in drinking-water below which no effects can be observed remains to be determined, and there is an urgent need for identification of the mechanism by which arsenic causes cancer, which appears to be the most sensitive toxicity end-point.

The practical quantification limit for arsenic is in the region of 1–10 µg/litre, and removal of arsenic to concentrations below 10 µg/litre is difficult in many circumstances. In view of the significant uncertainties surrounding the risk assessment for arsenic carcinogenicity and the practical difficulties in removing arsenic from drinking-water, the guideline value of 10 µg/litre is retained as a goal. In view of the scientific uncertainties, the guideline value is designated as provisional. In many countries, this guideline value may not be attainable; where this is the case, every effort should be made to keep concentrations as low as possible.

Practical considerations

A silver diethyldithiocarbamate spectrophotometric method is available for the determination of arsenic; the detection limit is about 1 µg/litre (ISO, 1982). Graphite furnace AAS, hydride generation AAS and ICP/MS are more sensitive. HPLC in combination with ICP/MS can also be used to determine various arsenic species.

It is technically feasible to achieve arsenic concentrations of 5 µg/litre or lower using any of several possible treatment methods. However, this requires careful process optimization and control, and a more reasonable expectation is that 10 µg/litre should be achievable by conventional treatment, e.g., coagulation (WHO, 2001). For local non-piped water supplies, the first option is often substitution by, or dilution with, microbiologically safe low-arsenic sources. It may also be appropriate to use alternative sources for drinking and cooking but to use the contaminated sources for purposes such as washing and laundry. There are also an increasing number of effective small-scale treatment techniques, usually based around coagulation and precipitation or adsorption, available at relatively low cost for removal of arsenic from small supplies.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* recommended a maximum allowable concentration of 0.2 mg/litre for arsenic, based on health concerns. In the 1963 *International Standards*, this value was lowered to 0.05 mg/litre, which was retained as a tentative upper concentration limit in the 1971 *International Standards*. The guideline value of 0.05 mg/litre was also retained in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984. A provisional guideline value for arsenic was set at the practical quantification limit of 0.01 mg/litre in the 1993 *Guidelines*, based on concern regarding its carcinogenicity in humans.

Assessment date

The risk assessment was conducted in 2003 for the third edition. An expanded summary statement based on the risk assessment was prepared in 2007 for the second addendum to the third edition.

Principal references

- IARC (1987) *Overall evaluations of carcinogenicity: An updating of IARC Monographs volumes 1–42*. Lyon, International Agency for Research on Cancer, pp. 100–106 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7).
- IPCS (2001) *Arsenic and arsenic compounds*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 224).
- ISO (1982) *Water quality – determination of total arsenic*. Geneva, International Organization for Standardization (ISO 6595-1982).
- USNRC (2001) *Arsenic in drinking water, 2001 update*. Washington, DC, United States National Research Council, National Academy Press.
- WHO (2001) Safe water technology. In: *United Nations synthesis report on arsenic in drinking-water* (draft). Geneva, World Health Organization (http://www.who.int/water_sanitation_health/dwq/arsenicun6.pdf).
- WHO (2003) *Arsenic in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/75).

12.9 Asbestos

Asbestos is introduced into water by the dissolution of asbestos-containing minerals and ores as well as from industrial effluents, atmospheric pollution and asbestos-cement pipes in the distribution system. Exfoliation of asbestos fibres from asbestos-cement pipes is related to the aggressiveness of the water supply. Limited data indicate that exposure to airborne asbestos released from tap water during showers or humidification is negligible.

Asbestos is a known human carcinogen by the inhalation route. Although well studied, there has been little convincing evidence of the carcinogenicity of ingested asbestos in epidemiological studies of populations with drinking-water supplies containing high concentrations of asbestos. Moreover, in extensive studies in animal species, asbestos has not consistently increased the incidence of tumours of the gastrointestinal tract. There is, therefore, no consistent evidence that ingested asbestos is hazardous to health, and thus it is concluded that there is no need to establish a health-based guideline value for asbestos in drinking-water.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to asbestos. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was noted that available data were insufficient to determine whether a guideline value was needed for asbestos. The 1993 Guidelines concluded that there was no consistent evidence that ingested asbestos was hazardous to health and that there was therefore no need to establish a health-based guideline value for asbestos in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Asbestos in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/2).

12.10 Atrazine

Atrazine (CAS No. 1912-24-9) is a selective pre- and early post-emergence herbicide. It has been found in surface water and groundwater as a result of its mobility in soil.

It is relatively stable in soil and aquatic environments, with a half-life measured in months, but is degraded by photolysis and microbial action in soil.

Guideline value	0.002 mg/litre
Occurrence	Found in groundwater and drinking-water at levels below 10 µg/litre
TDI	0.5 µg/kg of body weight based on a NOAEL of 0.5 mg/kg of body weight per day in a carcinogenicity study in the rat and an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 to reflect potential neoplasia)
Limit of detection	0.01 µg/litre by GC/MS
Treatment achievability	0.1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

The weight of evidence from a wide variety of genotoxicity assays indicates that atrazine is not genotoxic. There is evidence that atrazine can induce mammary tumours in rats. It is highly probable that the mechanism for this process is non-genotoxic. No significant increase in neoplasia has been observed in mice. IARC has concluded that atrazine is not classifiable as to its carcinogenicity in humans (Group 3).

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to atrazine, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Atrazine was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines established a health-based guideline value of 0.002 mg/litre for atrazine in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Atrazine in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/32).

12.11 Barium

Barium is present as a trace element in both igneous and sedimentary rocks, and barium compounds are used in a variety of industrial applications; however, barium in water comes primarily from natural sources. Food is the primary source of intake for the non-occupationally exposed population. However, where barium levels in water are high, drinking-water may contribute significantly to total intake.

Guideline value	0.7 mg/litre
Occurrence	Concentrations in drinking-water are generally below 100 µg/litre, although concentrations above 1 mg/litre have been measured in drinking-water derived from groundwater.
NOAEL in humans	7.3 mg/litre in the most sensitive epidemiological study conducted to date, in which there were no significant differences in blood pressure or in the prevalence of cardiovascular disease between a population drinking water containing a mean barium concentration of 7.3 mg/litre and one whose water contained a barium concentration of 0.1 mg/litre
Guideline derivation	Uncertainty factor of 10 for intraspecies variation applied to NOAEL in humans
Limit of detection	0.1 µg/litre by ICP/MS; 2 µg/litre by AAS; 3 µg/litre by ICP/optical emission spectroscopy
Treatment achievability	0.1 mg/litre should be achievable using either ion exchange or precipitation softening; other conventional processes are ineffective
Additional comments	The guideline value for barium is based on an epidemiological study in which no adverse effects were observed, although the study population was relatively small and the power of the study was limited. As a consequence, an uncertainty factor of 10 was applied to the level of barium in the drinking-water of the study population. However, the level at which effects would be seen may be significantly greater than this concentration, so the guideline value for barium may be highly conservative and the margin of safety is likely to be high.

Toxicological review

There is no evidence that barium is carcinogenic or mutagenic. Barium has been shown to cause nephropathy in laboratory animals, but the toxicological end-point of greatest concern to humans appears to be its potential to cause hypertension.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* did not refer to barium. The 1963 *International Standards* recommended a maximum allowable concentration of 1.0 mg/litre, based on health concerns. The 1971 *International Standards* stated that barium should be controlled in drinking-water, but that insufficient information was available to enable a tentative limit to be established. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was concluded that it was

not necessary to establish a guideline value for barium in drinking-water, as there was no firm evidence of any health effects associated with the normally low levels of barium in water. A health-based guideline value of 0.7 mg/litre was derived for barium in the 1993 Guidelines, based on concern regarding the potential of barium to cause hypertension.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- IPCS (2001) *Barium and barium compounds*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 33).
- WHO (2003) *Barium in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/76).

12.12 Bentazone

Bentazone (CAS No. 25057-89-0) is a broad-spectrum herbicide used for a variety of crops. Photodegradation occurs in soil and water; however, bentazone is very mobile in soil and moderately persistent in the environment. Bentazone has been reported to occur in surface water, groundwater and drinking-water at concentrations of a few micrograms per litre or less. Although it has been found in groundwater and has a high affinity for the water compartment, it does not seem to accumulate in the environment. Exposure from food is unlikely to be high.

Long-term studies conducted in rats and mice have not indicated a carcinogenic potential, and a variety of *in vitro* and *in vivo* assays have indicated that bentazone is not genotoxic. A health-based value of 300 µg/litre can be calculated on the basis of an ADI of 0.1 mg/kg of body weight established by JMPR, based on haematological effects observed in a 2-year dietary study in rats. However, because bentazone occurs at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a health-based guideline value.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to bentazone, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Bentazone was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines established a health-based guideline value of 0.03 mg/litre for bentazone, based on an ADI established by JMPR in 1991. This guideline value was amended to 0.3 mg/litre in the addendum to the Guidelines, published in 1998, based on new information on the environmental behaviour of bentazone and exposure from food.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- FAO/WHO (1999) *Pesticide residues in food – 1998. Evaluations – 1998. Part II – Toxicology*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/01.12).

WHO (2003) *Bentazone in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/77).

12.13 Benzene

Benzene is used principally in the production of other organic chemicals. It is present in petrol, and vehicular emissions constitute the main source of benzene in the environment. Benzene may be introduced into water by industrial effluents and atmospheric pollution.

Guideline value	0.01 mg/litre
Occurrence	Concentrations in drinking-water generally less than 5 µg/litre
Basis of guideline derivation	Robust linear extrapolation model (because of statistical lack of fit of some of the data with the linearized multistage model) applied to leukaemia and lymphomas in female mice and oral cavity squamous cell carcinomas in male rats in a 2-year gavage study in rats and mice
Limit of detection	0.2 µg/litre by GC with photoionization detection and confirmation by MS
Treatment achievability	0.01 mg/litre should be achievable using GAC or air stripping
Additional comments	Lower end of estimated range of concentrations in drinking-water corresponding to an upper-bound excess lifetime cancer risk of 10^{-5} (10–80 µg/litre) corresponds to the estimate derived from data on leukaemia from epidemiological studies involving inhalation exposure, which formed the basis for the previous guideline value. The previous guideline value is therefore retained.

Toxicological review

Acute exposure of humans to high concentrations of benzene primarily affects the central nervous system. At lower concentrations, benzene is toxic to the haematopoietic system, causing a continuum of haematological changes, including leukaemia. Because benzene is carcinogenic to humans, IARC has classified it in Group 1. Haematological abnormalities similar to those observed in humans have been observed in animal species exposed to benzene. In animal studies, benzene was shown to be carcinogenic following both inhalation and ingestion. It induced several types of tumours in both rats and mice in a 2-year carcinogenesis bioassay by gavage in corn oil. Benzene has not been found to be mutagenic in bacterial assays, but it has been shown to cause chromosomal aberrations *in vivo* in a number of species, including humans, and to be positive in the mouse micronucleus test.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to benzene. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.01 mg/litre was recommended for

benzene based on human leukaemia data from inhalation exposure applied to a linear multistage extrapolation model. The 1993 Guidelines estimated the range of benzene concentrations in drinking-water corresponding to an upper-bound excess lifetime cancer risk of 10^{-5} to be 0.01–0.08 mg/litre based on carcinogenicity in female mice and male rats. As the lower end of this estimate corresponds to the estimate derived from epidemiological data, which formed the basis for the previous guideline value of 0.01 mg/litre associated with a 10^{-5} upper-bound excess lifetime cancer risk, the guideline value of 0.01 mg/litre was retained.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Benzene in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/24).

12.14 Boron

Boron compounds are used in the manufacture of glass, soaps and detergents and as flame retardants. The general population obtains the greatest amount of boron through food intake, as it is naturally found in many edible plants. Boron is found naturally in groundwater, but its presence in surface water is frequently a consequence of the discharge of treated sewage effluent, in which it arises from use in some detergents, to surface waters.

Provisional guideline value	0.5 mg/litre The guideline is designated as provisional because it will be difficult to achieve in areas with high natural boron levels with the treatment technology available.
Occurrence	Concentrations vary widely and depend on the surrounding geology and wastewater discharges. For most of the world, the concentration range of boron in drinking-water is judged to be between 0.1 and 0.3 mg/litre.
TDI	0.16 mg/kg of body weight, based on a NOAEL of 9.6 mg/kg of body weight per day for developmental toxicity (decreased fetal body weight in rats) and an uncertainty factor of 60 (10 for interspecies variation and 6 for intraspecies variation)
Limit of detection	0.2 µg/litre by ICP/MS; 6–10 µg/litre by ICP/AES

Treatment achievability	Conventional water treatment (coagulation, sedimentation, filtration) does not significantly remove boron, and special methods need to be installed in order to remove boron from waters with high boron concentrations. Ion exchange and reverse osmosis processes may enable substantial reduction but are likely to be prohibitively expensive. Blending with low-boron supplies may be the only economical method to reduce boron concentrations in waters where these concentrations are high.
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

Short- and long-term oral exposures to boric acid or borax in laboratory animals have demonstrated that the male reproductive tract is a consistent target of toxicity. Testicular lesions have been observed in rats, mice and dogs given boric acid or borax in food or drinking-water. Developmental toxicity has been demonstrated experimentally in rats, mice and rabbits. Negative results in a large number of mutagenicity assays indicate that boric acid and borax are not genotoxic. In long-term studies in mice and rats, boric acid and borax caused no increase in tumour incidence.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to boron. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was concluded that no action was required for boron. A health-based guideline value of 0.3 mg/litre for boron was established in the 1993 Guidelines, while noting that boron's removal by drinking-water treatment appears to be poor. This guideline value was increased to 0.5 mg/litre in the addendum to the Guidelines published in 1998 and was designated as provisional because, with the treatment technology available, the guideline value will be difficult to achieve in areas with high natural boron levels.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Boron in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/54).

12.15 Bromate

Sodium and potassium bromate are powerful oxidizers used mainly in permanent wave neutralizing solutions and the dyeing of textiles using sulfur dyes. Potassium bromate is also used as an oxidizer to mature flour during milling, in treating barley in beer making and in fish paste products, although JECFA has concluded that the use of potassium bromate in food processing is not appropriate. Bromate is not normally found in water, but may be formed during ozonation when the bromide ion is present in water. Under certain conditions, bromate may also be formed in concentrated hypochlorite solutions used to disinfect drinking-water.

Provisional guideline value	0.01 mg/litre The guideline value is provisional because of limitations in available analytical and treatment methods.
Occurrence	Has been reported in drinking-water with a variety of source water characteristics after ozonation at concentrations ranging from <2 to 293 µg/litre, depending on bromide ion concentration, ozone dosage, pH, alkalinity and dissolved organic carbon; can also be formed in the electrolytic generation of chlorine and hypochlorite from brine with a high level of bromide contamination
Basis of guideline derivation	Upper-bound estimate of cancer potency for bromate is 0.19 per mg/kg of body weight per day, based on low-dose linear extrapolation (a one-stage Weibull time-to-tumour model was applied to the incidence of mesotheliomas, renal tubule tumours and thyroid follicular tumours in male rats given potassium bromate in drinking-water, using the 12-, 26-, 52- and 77-week interim kill data). A health-based value of 2 µg/litre is associated with the upper-bound excess cancer risk of 10 ⁻⁵ . A similar conclusion may be reached through several other methods of extrapolation, leading to values in the range 2–6 µg/litre.
Limit of detection	1.5 µg/litre by ion chromatography with suppressed conductivity detection; 0.2 µg/litre by ion chromatography with UV/visible absorbance detection; 0.3 µg/litre by ion chromatography with detection by ICP/MS
Treatment achievability	Bromate is difficult to remove once formed. By appropriate control of disinfection conditions, it is possible to achieve bromate concentrations below 0.01 mg/litre.

Toxicological review

IARC has concluded that although there is inadequate evidence of carcinogenicity in humans, there is sufficient evidence for the carcinogenicity of potassium bromate in experimental animals and has classified it in Group 2B (possibly carcinogenic to humans). Bromate is mutagenic both *in vitro* and *in vivo*. At this time, there is not sufficient evidence to conclude the mode of carcinogenic action for potassium bromate. Observation of tumours at a relatively early time and the positive response of bromate in a variety of genotoxicity assays suggest that the predominant mode of action at low doses is due to DNA reactivity. Although there is limited evidence to

suggest that the DNA reactivity in kidney tumours may have a non-linear dose–response relationship, there is no evidence to suggest that this same dose–response relationship operates in the development of mesotheliomas or thyroid tumours. Oxidative stress may play a role in the formation of kidney tumours, but the evidence is insufficient to establish lipid peroxidation and free radical production as key events responsible for induction of kidney tumours. Also, there are no data currently available to suggest that any single mechanism, including oxidative stress, is responsible for the production of thyroid and peritoneal tumours by bromate.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to bromate. The 1993 Guidelines calculated the concentration of bromate in drinking-water associated with an upper-bound excess lifetime cancer risk of 10^{-5} to be 0.003 mg/litre. However, because of limitations in available analytical and treatment methods, a provisional guideline value of 0.025 mg/litre, associated with an upper-bound excess lifetime cancer risk of 7×10^{-5} , was recommended.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Bromate in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/78).

12.16 Brominated acetic acids

Brominated acetic acids are formed during disinfection of water that contains bromide ions and organic matter. Bromide ions occur naturally in surface water and groundwater and exhibit seasonal fluctuations in levels. Bromide ion levels can increase due to saltwater intrusion resulting from drought conditions or due to pollution. Brominated acetates are generally present in surface water and groundwater distribution systems at mean concentrations below 5 µg/litre.

The database for dibromoacetic acid is considered inadequate for the derivation of a guideline value. There are no systemic toxicity studies of subchronic duration or longer. The database also lacks suitable toxicokinetic studies, a carcinogenicity study, a developmental study in a second species and a multigeneration reproductive toxicity study (one has been conducted but is currently being evaluated by the US EPA). Available mutagenicity data suggest that dibromoacetate is genotoxic.

Data are also limited on the oral toxicity of monobromoacetic acid and bromochloroacetic acid. Limited mutagenicity and genotoxicity data give mixed results for monobromoacetic acid and generally positive results for bromochloroacetic acid.

Data gaps include subchronic or chronic toxicity studies, multigeneration reproductive toxicity studies, standard developmental toxicity studies and carcinogenicity studies. The available data are considered inadequate to establish guideline values for these chemicals.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to brominated acetic acids. Brominated acetic acids were not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998.

Assessment date

The risk assessment was conducted in 2003.

Principal references

IPCS (2000) *Disinfectants and disinfectant by-products*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 216).

WHO (2003) *Brominated acetic acids in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/79).

12.17 Cadmium

Cadmium metal is used in the steel industry and in plastics. Cadmium compounds are widely used in batteries. Cadmium is released to the environment in wastewater, and diffuse pollution is caused by contamination from fertilizers and local air pollution. Contamination in drinking-water may also be caused by impurities in the zinc of galvanized pipes and solders and some metal fittings. Food is the main source of daily exposure to cadmium. The daily oral intake is 10–35 µg. Smoking is a significant additional source of cadmium exposure.

Guideline value	0.003 mg/litre
Occurrence	Levels in drinking-water usually less than 1 µg/litre
PTWI	7 µg/kg of body weight, on the basis that if levels of cadmium in the renal cortex are not to exceed 50 mg/kg, total intake of cadmium (assuming an absorption rate for dietary cadmium of 5% and a daily excretion rate of 0.005% of body burden) should not exceed 1 µg/kg of body weight per day
Limit of detection	0.01 µg/litre by ICP/MS; 2 µg/litre by FAAS
Treatment achievability	0.002 mg/litre should be achievable using coagulation or precipitation softening

Guideline derivation	
● allocation to water	10% of PTWI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	<ul style="list-style-type: none"> ● Although new information indicates that a proportion of the general population may be at increased risk for tubular dysfunction when exposed at the current PTWI, the risk estimates that can be made at present are imprecise. ● It is recognized that the margin between the PTWI and the actual weekly intake of cadmium by the general population is small, less than 10-fold, and that this margin may be even smaller in smokers.

Toxicological review

Absorption of cadmium compounds is dependent on the solubility of the compounds. Cadmium accumulates primarily in the kidneys and has a long biological half-life in humans of 10–35 years. There is evidence that cadmium is carcinogenic by the inhalation route, and IARC has classified cadmium and cadmium compounds in Group 2A. However, there is no evidence of carcinogenicity by the oral route and no clear evidence for the genotoxicity of cadmium. The kidney is the main target organ for cadmium toxicity. The critical cadmium concentration in the renal cortex that would produce a 10% prevalence of low-molecular-weight proteinuria in the general population is about 200 mg/kg and would be reached after a daily dietary intake of about 175 µg per person for 50 years.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* did not refer to cadmium. The 1963 International Standards recommended a maximum allowable concentration of 0.01 mg/litre, based on health concerns. This value was retained in the 1971 International Standards as a tentative upper concentration limit, based on the lowest concentration that could be conveniently measured. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 0.005 mg/litre was recommended for cadmium in drinking-water. This value was lowered to 0.003 mg/litre in the 1993 Guidelines, based on the PTWI set by JECFA.

Assessment date

The risk assessment was conducted in 2003.

Principal references

JECFA (2000) *Summary and conclusions of the fifty-fifth meeting, Geneva, 6–15 June 2000*. Geneva, World Health Organization, Joint FAO/WHO Expert Committee on Food Additives.

WHO (2003) *Cadmium in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/80).

12.17(a) Carbaryl

Carbaryl (CAS No. 63-25-2) is a broad-spectrum carbamate insecticide that is used to control insect pests in crops, trees and ornamental plants. It also has some uses in public health and veterinary practice. Carbaryl has not been reported in drinking-water; however, it could occur following overspraying or spillage into surface water. Exposure through drinking-water is, therefore, considered to be low unless in exceptional circumstances. The major route of carbaryl intake for the general population is food, but residues are considered to be relatively low.

Carbaryl acts through inhibition of brain cholinesterase, and this is also its primary mode of toxicity. However, carbaryl is also considered to be a non-genotoxic carcinogen in mice, in which it causes vascular tumours in males. On this basis, JMPR established an ADI of 0–0.008 mg/kg of body weight. This was based on a LOAEL of 15 mg/kg of body weight per day and application of a safety factor of 2000 ($\times 10$ for interspecies variation, $\times 10$ for intraspecies variation and $\times 20$ to reflect the occurrence of the rare and malignant tumour for which a no-effect level could not be identified).

A health-based value of 50 $\mu\text{g/litre}$ (rounded value) can be determined from the JMPR ADI of 0–0.008 mg/kg of body weight, assuming a 60-kg adult drinking 2 litres of water per day and allowing 20% of the ADI from drinking-water. However, carbaryl does not appear to be found in drinking-water at significant concentrations, and so it is not considered necessary to propose a formal guideline value.

History of guideline development

Carbaryl was not evaluated in the WHO *International Standards for Drinking-water* or in the first or second editions of the WHO *Guidelines for Drinking-water Quality*.

Assessment date

The risk assessment was conducted in 2006.

Principal references

FAO/WHO (2002) *Pesticide residues in food – 2001. Toxicological evaluations. Carbaryl (addendum)*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (<http://www.inchem.org/documents/jmpr/jmpmono/2001pr02.htm>).

WHO (2008) *Carbaryl in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/HSE/AMR/08.03/5).

12.18 Carbofuran

Carbofuran (CAS No. 1563-66-2) is used worldwide as a pesticide for many crops. Residues in treated crops are generally very low or not detectable. The physical and chemical properties of carbofuran and the few data on occurrence indicate that drinking-water from both groundwater and surface water sources is potentially the major route of exposure.

Guideline value	0.007 mg/litre
Occurrence	Has been detected in surface water, groundwater and drinking-water, generally at levels of a few micrograms per litre or lower; highest concentration (30 µg/litre) measured in groundwater
ADI	0.002 mg/kg of body weight based on a NOAEL of 0.22 mg/kg of body weight per day for acute (reversible) effects in dogs in a short-term (4-week) study conducted as an adjunct to a 13-week study in which inhibition of erythrocyte acetylcholinesterase activity was observed, and using an uncertainty factor of 100
Limit of detection	0.1 µg/litre by GC with a nitrogen–phosphorus detector; 0.9 µg/litre by reverse-phase HPLC with a fluorescence detector
Treatment achievability	1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of ADI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	Use of a 4-week study was considered appropriate because the NOAEL is based on a reversible acute effect; the NOAEL will also be protective for chronic effects.

Toxicological review

Carbofuran is highly toxic after acute oral administration. The main systemic effect of carbofuran poisoning in short- and long-term toxicity studies appears to be cholinesterase inhibition. No evidence of teratogenicity has been found in reproductive toxicity studies. On the basis of available studies, carbofuran does not appear to be carcinogenic or genotoxic.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to carbofuran, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Carbofuran was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but a

health-based guideline value of 0.005 mg/litre was established for carbofuran in the 1993 Guidelines, based on human data and supported by observations in laboratory animals. This value was amended to 0.007 mg/litre in the addendum to the Guidelines published in 1998, on the basis of the ADI established by JMPR in 1996.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal references

FAO/WHO (1997) *Pesticide residues in food – 1996. Evaluations – 1996. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/97.1).

WHO (2003) *Carbofuran in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/81).

12.19 Carbon tetrachloride

Carbon tetrachloride is used mainly in the production of chlorofluorocarbon refrigerants, foam-blowing agents and solvents. However, since the Montreal Protocol on Substances that Deplete the Ozone Layer (1987) and its amendments (1990 and 1992) established a timetable for the phase-out of the production and consumption of carbon tetrachloride, manufacture and use have dropped and will continue to drop. Carbon tetrachloride is released mostly into the atmosphere but also into industrial wastewater. Although it readily migrates from surface water to the atmosphere, levels in anaerobic groundwater may remain elevated for months or even years. Although available data on concentrations in food are limited, the intake from air is expected to be much greater than that from food or drinking-water.

Guideline value	0.004 mg/litre
Occurrence	Concentrations in drinking-water generally less than 5 µg/litre
TDI	1.4 µg/kg of body weight, based on a NOAEL of 1 mg/kg of body weight per day for hepatotoxic effects in a 12-week oral gavage study in rats, incorporating a conversion factor of 5/7 for daily dosing and applying an uncertainty factor of 500 (100 for inter- and intraspecies variation, 10 for the duration of the study and a modifying factor of 0.5 because it was a bolus study)
Limit of detection	0.1–0.3 µg/litre by GC with ECD or MS
Treatment achievability	0.001 mg/litre should be achievable using air stripping

Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	The guideline value is lower than the range of values associated with upper-bound lifetime excess cancer risks of 10^{-4} , 10^{-5} and 10^{-6} calculated by linear extrapolation.

Toxicological review

The primary targets for carbon tetrachloride toxicity are liver and kidney. In experiments with mice and rats, carbon tetrachloride proved to be capable of inducing hepatomas and hepatocellular carcinomas. The doses inducing hepatic tumours were higher than those inducing cell toxicity. It is likely that the carcinogenicity of carbon tetrachloride is secondary to its hepatotoxic effects. On the basis of available data, carbon tetrachloride can be considered to be a non-genotoxic compound. Carbon tetrachloride is classified by IARC as being possibly carcinogenic to humans (Group 2B): there is sufficient evidence that carbon tetrachloride is carcinogenic in laboratory animals, but inadequate evidence in humans.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to carbon tetrachloride. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a tentative guideline value of 0.003 mg/litre was recommended; the guideline was designated as tentative because reliable evidence on which to calculate a guideline value based on carcinogenicity was available in only one animal species, because of the good qualitative supporting data and because of its frequency of occurrence in water. The 1993 Guidelines established a health-based guideline value of 0.002 mg/litre for carbon tetrachloride.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- IPCS (1999) *Carbon tetrachloride*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 208).
- WHO (2003) *Carbon tetrachloride in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/82).

12.20 Chloral hydrate (trichloroacetaldehyde)

Chloral hydrate can be formed as a by-product of the chlorination of water containing organic precursor material, such as fulvic and humic acids. It has been found in drinking-water at concentrations of up to 100 µg/litre, but concentrations are usually

below 10 µg/litre. Concentrations are generally higher in surface water than in groundwater, and concentrations appear to increase during distribution.

Chloral hydrate is used as an intermediate in the production of insecticides, herbicides and hypnotic drugs. It has also been widely used as a sedative or hypnotic drug in humans at oral doses of up to about 750–1000 mg/day. Although intake from clinical use is considerably higher than intake from drinking-water, clinical exposure is of shorter-term duration.

No epidemiological or carcinogenic studies were found in humans that associated exposure to chloral hydrate with cancer, despite the fact that chloral hydrate has been used for many decades (and still is used) as a sedative and hypnotic drug in adults and children (specifically for dental procedures). IARC classified chloral hydrate as not classifiable as to its carcinogenicity to humans (Group 3), based on inadequate evidence in humans and limited evidence in experimental animals. There is equivocal evidence of genotoxicity for chloral hydrate.

A health-based value of 0.1 mg/litre (rounded figure) can be calculated on the basis of a TDI of 0.0045 mg/kg of body weight per day derived based on an increased incidence of liver histopathology observed in B6C3F1 mice in a 2-year drinking-water study, allocating 80% of the TDI to drinking-water (because most exposure to chloral hydrate is from drinking-water) and assuming a 60-kg adult consuming 2 litres of water per day. However, because chloral hydrate usually occurs in drinking-water at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a guideline value.

Chloral hydrate levels in drinking-water can be controlled by changes to disinfection practice (e.g., enhanced coagulation and softening to remove organic precursor compounds, moving the point of disinfection to reduce the reaction between chlorine and precursor compounds and using chloramines for residual disinfection instead of chlorine) and by GAC treatment.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to chloral hydrate. The 1993 Guidelines established a provisional health-based guideline value of 0.01 mg/litre for chloral hydrate in drinking-water. The guideline value was designated as provisional because of the limitations of the available database, necessitating the use of an uncertainty factor of 10 000. This guideline value was brought forward to the third edition of the Guidelines.

Assessment date

The risk assessment was conducted in 2004.

Principal references

IPCS (2000) *Chloral hydrate*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 25).

IPCS (2000) *Disinfectants and disinfectant by-products*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 216).

WHO (2005) *Chloral hydrate in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/49).

12.21 Chlordane

Chlordane (CAS No. 57-47-9) is a broad-spectrum insecticide that has been used since 1947. Its use has recently been increasingly restricted in many countries, and it is now used mainly to destroy termites by subsurface injection into soil. Chlordane may be a low-level source of contamination of groundwater when applied by subsurface injection. Technical chlordane is a mixture of compounds, with the *cis* and *trans* forms of chlordane predominating. It is very resistant to degradation, is highly immobile in soil and it unlikely to migrate to groundwater, where it has only rarely been found. It is readily lost to the atmosphere. Although levels of chlordane in food have been decreasing, it is highly persistent and has a high bioaccumulation potential.

Guideline value	0.0002 mg/litre (0.2 µg/litre)
Occurrence	Has been detected in both drinking-water and groundwater, usually at levels below 0.1 µg/litre
PTDI	0.5 µg/kg of body weight based on a NOAEL of 50 µg/kg of body weight per day for increased liver weights, serum bilirubin levels and incidence of hepatocellular swelling, derived from a long-term dietary study in rats, and using an uncertainty factor of 100
Limit of detection	0.014 µg/litre by GC with an ECD
Treatment achievability	0.1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	1% of PTDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	Chlordane is listed under the Stockholm Convention on Persistent Organic Pollutants. Hence, monitoring may occur in addition to that required by drinking-water guidelines.

Toxicological review

In experimental animals, prolonged exposure in the diet causes liver damage. Chlordane produces liver tumours in mice, but the weight of evidence indicates that it is not genotoxic. Chlordane can interfere with cell communication *in vitro*, a characteristic of many tumour promoters. IARC re-evaluated chlordane in 1991 and concluded that there is inadequate evidence for its carcinogenicity in humans and sufficient evidence for its carcinogenicity in animals, classifying it in Group 2B.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to chlordane, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.3 µg/litre was recommended for chlordane (total isomers), based on the

ADI recommended by JMPR in 1977. The 1993 Guidelines established a health-based guideline value of 0.2 µg/litre for chlordane in drinking-water, based on an ADI established by JMPR in 1986.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (1995) *Pesticide residues in food – 1994. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment Groups*. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper 127).

WHO (2003) *Chlordane in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/84).

12.22 Chloride

Chloride in drinking-water originates from natural sources, sewage and industrial effluents, urban runoff containing de-icing salt and saline intrusion.

The main source of human exposure to chloride is the addition of salt to food, and the intake from this source is usually greatly in excess of that from drinking-water.

Excessive chloride concentrations increase rates of corrosion of metals in the distribution system, depending on the alkalinity of the water. This can lead to increased concentrations of metals in the supply.

No health-based guideline value is proposed for chloride in drinking-water. However, chloride concentrations in excess of about 250 mg/litre can give rise to detectable taste in water (see chapter 10).

History of guideline development

The 1958 WHO *International Standards for Drinking-water* suggested that concentrations of chloride greater than 600 mg/litre would markedly impair the potability of the water. The 1963 and 1971 *International Standards* retained this value as a maximum allowable or permissible concentration. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 250 mg/litre was established for chloride, based on taste considerations. No health-based guideline value for chloride in drinking-water was proposed in the 1993 Guidelines, although it was confirmed that chloride concentrations in excess of about 250 mg/litre can give rise to detectable taste in water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chloride in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/3).

12.23 Chlorine

Chlorine is produced in large amounts and widely used both industrially and domestically as an important disinfectant and bleach. In particular, it is widely used in the disinfection of swimming pools and is the most commonly used disinfectant and oxidant in drinking-water treatment. In water, chlorine reacts to form hypochlorous acid and hypochlorites.

Guideline value	5 mg/litre
Occurrence	Present in most disinfected drinking-water at concentrations of 0.2–1 mg/litre
TDI	150 µg/kg of body weight, derived from a NOAEL for the absence of toxicity in rodents ingesting chlorine in drinking-water for 2 years
Limit of detection	0.01 µg/litre following pre-column derivatization to 4-bromoacetanilide by HPLC; 10 µg/litre as free chlorine by colorimetry; 0.2 mg/litre by ion chromatography
Treatment achievability	It is possible to reduce the concentration of chlorine effectively to zero (< 0.1 mg/litre) by reduction. However, it is normal practice to supply water with a chlorine residual of a few tenths of a milligram per litre to act as a preservative during distribution.
Guideline derivation	
● allocation to water	100% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	<ul style="list-style-type: none"> ● The guideline value is conservative, as no adverse effect level was identified in the critical study. ● Most individuals are able to taste chlorine at the guideline value.

Toxicological review

In humans and animals exposed to chlorine in drinking-water, no specific adverse treatment-related effects have been observed. IARC has classified hypochlorite in Group 3.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to chlorine. The 1993 Guidelines established a guideline value of 5 mg/litre for free chlorine in drinking-water, but noted that this value is conservative, as no adverse effect level was identified in the study used. It was also noted that most individuals are able to taste chlorine at the guideline value.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chlorine in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/45).

12.24 Chlorite and chlorate

Chlorite and chlorate are DBPs resulting from the use of chlorine dioxide as a disinfectant and for odour/taste control in water. Chlorine dioxide is also used as a bleaching agent for cellulose, paper pulp, flour and oils. Sodium chlorite and sodium chlorate are both used in the production of chlorine dioxide as well as for other commercial purposes. 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. The major route of environmental exposure to chlorine dioxide, sodium chlorite and sodium chlorate is through drinking-water.

Provisional guideline values

Chlorite	0.7 mg/litre
Chlorate	0.7 mg/litre

The guideline values for chlorite and chlorate are designated as provisional because use of chlorine dioxide as a disinfectant may result in the chlorite and chlorate guideline values being exceeded, and difficulties in meeting the guideline value must never be a reason for compromising adequate disinfection.

Occurrence	Levels of chlorite in water reported in one study ranged from 3.2 to 7.0 mg/litre; however, the combined levels will not exceed the dose of chlorine dioxide applied. Chlorate can also form in hypochlorite solutions on storage.
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12. CHEMICAL FACT SHEETS

TDIs	
Chlorite	30 µg/kg of body weight based on a NOAEL of 2.9 mg/kg of body weight per day identified in a two-generation study in rats, based on lower startle amplitude, decreased absolute brain weight in the F ₁ and F ₂ generations and altered liver weights in two generations, using an uncertainty factor of 100 (10 each for inter- and intraspecies variation)
Chlorate	30 µg/kg of body weight based on a NOAEL of 30 mg/kg of body weight per day in a recent well conducted 90-day study in rats, based on thyroid gland colloid depletion at the next higher dose, and using an uncertainty factor of 1000 (10 each for inter- and intraspecies variation and 10 for the short duration of the study)
Limit of detection	5 µg/litre by ion chromatography with suppressed conductivity detection for chlorate
Treatment achievability	It is possible to reduce the concentration of chlorine dioxide effectively to zero (< 0.1 mg/litre) by reduction; however, it is normal practice to supply water with a chlorine dioxide residual of a few tenths of a milligram per litre to act as a preservative during distribution. Chlorate concentrations arising from the use of sodium hypochlorite are generally around 0.1 mg/litre, although concentrations above 1 mg/litre have been reported. With chlorine dioxide disinfection, the concentration of chlorate depends heavily on process conditions (in both the chlorine dioxide generator and the water treatment plant) and applied dose of chlorine dioxide. As there is no viable option for reducing chlorate concentrations, control of chlorate concentration must rely on preventing its addition (from sodium hypochlorite) or formation (from chlorine dioxide). Chlorite ion is an inevitable by-product arising from the use of chlorine dioxide. When chlorine dioxide is used as the final disinfectant at typical doses, the resulting chlorite concentration should be <0.2 mg/litre. If chlorine dioxide is used as a pre-oxidant, the resulting chlorite concentration may need to be reduced using ferrous iron or activated carbon.
Guideline derivation	
● allocation to water	80% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

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 hydrolysis to chlorite and because the chlorite provisional guideline value is adequately protective for potential toxicity from chlorine dioxide. The taste and odour threshold for this compound is 0.4 mg/litre.

Chlorite

IARC has concluded that chlorite is not classifiable as to its carcinogenicity to humans. The primary and most consistent finding arising from exposure to chlorite is oxidative stress resulting in changes in the red blood cells. This end-point is seen in laboratory animals and, by analogy with chlorate, in humans exposed to high doses in poisoning incidents. Studies with human volunteers for up to 12 weeks did not identify any effect on blood parameters at the highest dose tested, 36 µg/kg of body weight per day.

Chlorate

Like chlorite, the primary concern with chlorate is oxidative damage to red blood cells. Also like chlorite, a chlorate dose of 36 µg/kg of body weight per day for 12 weeks did not result in any adverse effects in human volunteers. Although the database for chlorate is less extensive than that for chlorite, a recent well conducted 90-day study in rats is available. A long-term study is in progress, which should provide more information on chronic exposure to chlorate.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to chlorine dioxide, chlorate or chlorite. The 1993 Guidelines established a provisional health-based guideline value of 0.2 mg/litre for chlorite in drinking-water. The guideline value was 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 disinfection. The 1993 Guidelines did not establish a health-based guideline value for chlorine dioxide in drinking-water because of its rapid breakdown and because the provisional guideline value for chlorite is adequately protective for potential toxicity from chlorine dioxide. The 1993 Guidelines concluded that available data on the effects of chlorate in humans and experimental animals are insufficient to permit development of a guideline value and recommended that further research was needed to characterize the non-lethal effects of chlorate. It was noted that the taste and odour threshold for chlorine dioxide is 0.4 mg/litre.

Assessment date

The risk assessment was conducted in 2003.

Principal references

IPCS (2000) *Disinfectants and disinfectant by-products*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 216).

WHO (2003) *Chlorite and chlorate in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/86).

12.25 Chloroacetones

1,1-Dichloroacetone is formed from the reaction between chlorine and organic precursors and has been detected in chlorinated drinking-water. Concentrations are estimated to be less than 10 µg/litre and usually less than 1 µg/litre.

The toxicological data on 1,1-dichloroacetone are very limited, although studies with single doses indicate that it affects the liver.

There are insufficient data at present to permit the proposal of guideline values for 1,1-dichloroacetone or any of the other chloroacetones.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to chloroacetones. The 1993 Guidelines concluded that there were insufficient data available to permit the proposal of guideline values for any of the chloroacetones.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chloroacetones in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/50).

12.26 Chlorophenols (2-chlorophenol, 2,4-dichlorophenol, 2,4,6-trichlorophenol)

Chlorophenols are present in drinking-water as a result of the chlorination of phenols, as by-products of the reaction of hypochlorite with phenolic acids, as biocides or as degradation products of phenoxy herbicides. Those most likely to occur in drinking-water as by-products of chlorination are 2-chlorophenol, 2,4-dichlorophenol and 2,4,6-trichlorophenol. The taste thresholds for chlorophenols in drinking-water are low.

Guideline value for 2,4,6-trichlorophenol	0.2 mg/litre
Occurrence	Concentrations of chlorophenols in drinking-water are usually less than 1 µg/litre.
Basis of guideline derivation	Applying the linearized multistage model to leukaemias in male rats observed in a 2-year feeding study (hepatic tumours found in this study were not used for risk estimation because of the possible role of contaminants in their induction)
Limit of detection	0.5–5 µg/litre by formation of pentafluorobenzyl ether derivatives; 1–10 µg/litre (monochlorophenols), 0.5 µg/litre (dichlorophenols) and 0.01 µg/litre (trichlorophenols) using GC with ECD
Treatment achievability	2,4,6-Trichlorophenol concentrations are generally less than 1 µg/litre. If necessary, 2,4,6-trichlorophenol concentrations can be reduced using GAC.
Additional comments	The guideline value for 2,4,6-trichlorophenol exceeds its lowest reported taste threshold.

Toxicological review

2-Chlorophenol

Data on the toxicity of 2-chlorophenol are limited. Therefore, no health-based guideline value has been derived.

2,4-Dichlorophenol

Data on the toxicity of 2,4-dichlorophenol are limited. Therefore, no health-based guideline value has been derived.

2,4,6-Trichlorophenol

2,4,6-Trichlorophenol has been reported to induce lymphomas and leukaemias in male rats and hepatic tumours in male and female mice. 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* studies. IARC has classified 2,4,6-trichlorophenol in Group 2B.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to chlorophenols. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline values for 2-chlorophenol, 4-chlorophenol, 2,4-dichlorophenol, 2,6-dichlorophenol or 2,4,5-trichlorophenol were recommended after a detailed evaluation of the compounds, although it was suggested that individual chlorophenols should not be present in drinking-water at a level above 0.0001 mg/litre for organoleptic reasons (and the total phenol content of water to be chlorinated should be kept below 0.001 mg/litre). In the same edition, a health-based guideline value of 0.01 mg/litre was recommended for 2,4,6-trichlorophenol, while noting

that the linear multistage extrapolation model appropriate for chemical carcinogens that was used in its derivation involved considerable uncertainty. It was also noted that 2,4,6-trichlorophenol may be detected by its taste and odour at a concentration of 0.0001 mg/litre. No health-based guidelines for 2-chlorophenol or 2,4-dichlorophenol were derived in the 1993 Guidelines, as data on their toxicity were limited. A guideline value of 0.2 mg/litre, associated with a 10^{-5} upper-bound excess lifetime cancer risk, was calculated for 2,4,6-trichlorophenol. This concentration exceeds the lowest reported taste threshold for the chemical (0.002 mg/litre).

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chlorophenols in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/47).

12.27 Chloropicrin

Chloropicrin, or trichloronitromethane, is formed by the reaction of chlorine with humic and amino acids and with nitrophenols. Its formation is increased in the presence of nitrates. Limited data from the USA indicate that concentrations in drinking-water are usually less than 5 µg/litre.

Decreased survival and body weights have been reported following long-term oral exposure in laboratory animals. Chloropicrin has been shown to be mutagenic in bacterial tests and in *in vitro* assays in lymphocytes. Because of the high mortality in a carcinogenesis bioassay and the limited number of end-points examined in the 78-week toxicity study, the available data were considered inadequate to permit the establishment of a guideline value for chloropicrin.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to chloropicrin. The 1993 Guidelines considered the available data to be inadequate to permit the establishment of a guideline value for chloropicrin in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chloropicrin in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/52).

12.28 Chlorotoluron

Chlorotoluron (CAS No. 15545-48-9) is a pre- or early post-emergence herbicide that is slowly biodegradable and mobile in soil. There is only very limited exposure to this compound from food.

Guideline value	0.03 mg/litre
Occurrence	Detected in drinking-water at concentrations of less than 1 µg/litre
TDI	11.3 µg/kg of body weight, derived from a NOEL of 11.3 mg/kg of body weight per day for systemic effects in a 2-year feeding study in mice using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for evidence of carcinogenicity)
Limit of detection	0.1 µg/litre by separation by reverse-phase HPLC followed by UV and electrochemical detection
Treatment achievability	0.1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

Chlorotoluron is of low toxicity in single, short-term and long-term exposures in animals, but it has been shown to cause an increase in adenomas and carcinomas of the kidneys of male mice given high doses for 2 years. As no carcinogenic effects were reported in a 2-year study in rats, it has been suggested that chlorotoluron has a carcinogenic potential that is both species- and sex-specific. Chlorotoluron and its metabolites have shown no evidence of genotoxicity.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to chlorotoluron, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Chlorotoluron was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 *Guidelines* established a health-based guideline value of 0.03 mg/litre for chlorotoluron in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chlorotoluron in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/33).

12.29 Chlorpyrifos

Chlorpyrifos (CAS No. 2921-88-2) is a broad-spectrum organophosphorus insecticide used for the control of mosquitos, flies, various crop pests in soil and on foliage, household pests and aquatic larvae. Although it is not recommended for addition to water for public health purposes by WHOPEs, it may be used in some countries as an aquatic larvicide for the control of mosquito larvae. Chlorpyrifos is strongly absorbed by soil and does not readily leach from it, degrading slowly by microbial action. It has a low solubility in water and great tendency to partition from aqueous into organic phases in the environment.

Guideline value	0.03 mg/litre
Occurrence	Detected in surface waters in USA, usually at concentrations below 0.1 µg/litre; also detected in groundwater in less than 1% of the wells tested, usually at concentrations below 0.01 µg/litre
ADI	0.01 mg/kg of body weight on the basis of a NOAEL of 1 mg/kg of body weight per day for inhibition of brain acetylcholinesterase activity in studies in mice, rats and dogs, using a 100-fold uncertainty factor, and on the basis of a NOAEL of 0.1 mg/kg of body weight per day for inhibition of erythrocyte acetylcholinesterase activity in a study of human subjects exposed for 9 days, using a 10-fold uncertainty factor
Limit of detection	1 µg/litre by GC using an ECD or flame photometric detection
Treatment achievability	No data available; should be amenable to treatment by coagulation (10–20% removal), activated carbon adsorption and ozonation
Guideline derivation	
● allocation to water	10% of ADI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

JMPR concluded that chlorpyrifos is unlikely to pose a carcinogenic risk to humans. Chlorpyrifos was not genotoxic in an adequate range of studies *in vitro* and *in vivo*. In long-term studies, inhibition of cholinesterase activity was the main toxicological finding in all species.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to chlorpyrifos, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Chlorpyrifos was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (2000) *Pesticide residues in food – 1999 evaluations. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/00.4).

WHO (2003) *Chlorpyrifos in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/87).

12.30 Chromium

Chromium is widely distributed in the Earth's crust. It can exist in valences of +2 to +6. In general, food appears to be the major source of intake.

Provisional guideline value	0.05 mg/litre for total chromium The guideline value is designated as provisional because of uncertainties in the toxicological database.
Occurrence	Total chromium concentrations in drinking-water are usually less than 2 µg/litre, although concentrations as high as 120 µg/litre have been reported.
Basis of guideline value derivation	There are no adequate toxicity studies available to provide a basis for a NOAEL. The guideline value was first proposed in 1958 for hexavalent chromium, based on health concerns, but was later changed to a guideline for total chromium because of difficulties in analysing for the hexavalent form only.
Limit of detection	0.05–0.2 µg/litre for total chromium by AAS
Treatment achievability	0.015 mg/litre should be achievable using coagulation

Toxicological review

In a long-term carcinogenicity study in rats given chromium(III) by the oral route, no increase in tumour incidence was observed. In rats, chromium(VI) is a carcinogen via the inhalation route, although the limited data available do not show evidence

for carcinogenicity via the oral route. In epidemiological studies, an association has been found between exposure to chromium(VI) by the inhalation route and lung cancer. IARC has classified chromium(VI) in Group 1 (human carcinogen) and chromium(III) in Group 3. Chromium(VI) compounds are active in a wide range of *in vitro* and *in vivo* genotoxicity tests, whereas chromium(III) compounds are not.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* recommended a maximum allowable concentration of 0.05 mg/litre for chromium (hexavalent), based on health concerns. This value was retained in the 1963 International Standards. Chromium was not evaluated in the 1971 International Standards. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, the guideline value of 0.05 mg/litre for total chromium was retained; total chromium was specified because of difficulties in analysing for the hexavalent form only. The 1993 Guidelines questioned the guideline value of 0.05 mg/litre because of the carcinogenicity of hexavalent chromium by the inhalation route and its genotoxicity, although the available toxicological data did not support the derivation of a new value. As a practical measure, 0.05 mg/litre, which is considered to be unlikely to give rise to significant health risks, was retained as the provisional guideline value until additional information becomes available and chromium can be re-evaluated.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chromium in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/4).

12.31 Copper

Copper is both an essential nutrient and a drinking-water contaminant. It has many commercial uses. It is used to make pipes, valves and fittings and is present in alloys and coatings. Copper sulfate pentahydrate is sometimes added to surface water for the control of algae. Copper concentrations in drinking-water vary widely, with the primary source most often being the corrosion of interior copper plumbing. Levels in running or fully flushed water tend to be low, whereas those in standing or partially flushed water samples are more variable and can be substantially higher (frequently > 1 mg/litre). Copper concentrations in treated water often increase during distribution, especially in systems with an acid pH or high-carbonate waters with an alkaline pH. Food and water are the primary sources of copper exposure in developed

countries. Consumption of standing or partially flushed water from a distribution system that includes copper pipes or fittings can considerably increase total daily copper exposure, especially for infants fed formula reconstituted with tap water.

Guideline value	2 mg/litre
Occurrence	Concentrations in drinking-water range from ≤ 0.005 to >30 mg/litre, primarily as a result of the corrosion of interior copper plumbing.
Basis of guideline derivation	To be protective against acute gastrointestinal effects of copper and provide an adequate margin of safety in populations with normal copper homeostasis
Limit of detection	0.02–0.1 $\mu\text{g/litre}$ by ICP/MS; 0.3 $\mu\text{g/litre}$ by ICP/optical emission spectroscopy; 0.5 $\mu\text{g/litre}$ by FAAS
Treatment achievability	Copper is not removed by conventional treatment processes. However, copper is not normally a raw water contaminant.
Additional comments	<ul style="list-style-type: none"> • For adults with normal copper homeostasis, the guideline value should permit consumption of 2 or 3 litres of water per day, use of a nutritional supplement and copper from foods without exceeding the tolerable upper intake level of 10 mg/day or eliciting an adverse gastrointestinal response. • Staining of laundry and sanitary ware occurs at copper concentrations above 1 mg/litre. At levels above 2.5 mg/litre, copper imparts an undesirable bitter taste to water; at higher levels, the colour of water is also impacted. • In most instances where copper tubing is used as a plumbing material, concentrations of copper will be below the guideline value. However, there are some conditions, such as highly acidic or aggressive waters, that will give rise to much higher copper concentrations, and the use of copper tubing may not be appropriate in such circumstances.

Toxicological review

IPCS concluded that the upper limit of the acceptable range of oral intake in adults is uncertain but is most likely in the range of several (more than 2 or 3) but not many milligrams per day in adults. This evaluation was based solely on studies of gastrointestinal effects of copper-contaminated drinking-water. The available data on toxicity in animals were not considered helpful in establishing the upper limit of the acceptable range of oral intake due to uncertainty about an appropriate model for humans, but they help to establish a mode of action for the response. The data on the gastrointestinal effects of copper must be used with caution, since the effects observed are influenced by the concentration of ingested copper to a greater extent than the total mass or dose ingested in a 24-h period. Recent studies have delineated the threshold for the effects of copper in drinking-water on the gastrointestinal tract, but there is still some uncertainty regarding the long-term effects of copper on sensitive populations, such as carriers of the gene for Wilson disease and other metabolic disorders of copper homeostasis.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* suggested that concentrations of copper greater than 1.5 mg/litre would markedly impair the potability of the water. The 1963 and 1971 International Standards retained this value as a maximum allowable or permissible concentration. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 1.0 mg/litre was established for copper, based on its laundry and other staining properties. The 1993 Guidelines derived a provisional health-based guideline value of 2 mg/litre for copper from the PMTDI proposed by JECFA, based on a rather old study in dogs that did not take into account differences in copper metabolism between infants and adults. The guideline value was considered provisional because of the uncertainties regarding copper toxicity in humans. This guideline value was retained in the addendum to the Guidelines published in 1998 and remained provisional as a result of uncertainties in the dose-response relationship between copper in drinking-water and acute gastrointestinal effects in humans. It was stressed that the outcome of epidemiological studies in progress in Chile, Sweden and the USA may permit more accurate quantification of effect levels for copper-induced toxicity in humans, including sensitive subpopulations. Copper can also give rise to taste problems at concentrations above 5 mg/litre and can stain laundry and sanitary ware at concentrations above 1 mg/litre.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- IPCS (1998) *Copper*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 200).
- WHO (2003) *Copper in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/88).

12.32 Cyanazine

Cyanazine (CAS No. 21725-46-2) is a member of the triazine family of herbicides. It is used as a pre- and post-emergence herbicide for the control of annual grasses and broadleaf weeds. It can be degraded in soil and water by microorganisms and by hydrolysis.

Guideline value	0.0006 mg/litre (0.6 µg/litre)
Occurrence	Has been detected in surface water and groundwater, usually at concentrations of a few micrograms per litre, although levels as high as 1.3 and 3.5 mg/litre have been measured in surface water and groundwater, respectively

TDI	0.198 µg/kg of body weight based on a NOAEL of 0.198 mg/kg of body weight for hyperactivity in male rats in a 2-year toxicity/carcinogenicity study, with an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for limited evidence of carcinogenicity)
Limit of detection	0.01 µg/litre by GC with MS
Treatment achievability	0.1 µg/litre should be achievable using GAC
Guideline derivation	
• allocation to water	10% of TDI
• weight	60-kg adult
• consumption	2 litres/day

Toxicological review

On the basis of the available mutagenicity data on cyanazine, evidence for genotoxicity is equivocal. Cyanazine causes mammary gland tumours in Sprague-Dawley rats but not in mice. The mechanism of mammary gland tumour development in Sprague-Dawley rats is currently under investigation and may prove to be hormonal (cf. atrazine). Cyanazine is also teratogenic in Fischer 344 rats at dose levels of 25 mg/kg of body weight per day and higher.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to cyanazine, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline value for triazine herbicides, which include cyanazine, was recommended after a detailed evaluation of the compounds. Cyanazine was not evaluated in the second edition of the *Guidelines for Drinking-water Quality*, published in 1993. In the addendum to the second edition of these Guidelines, published in 1998, a health-based guideline value of 0.6 µg/litre was established for cyanazine in drinking-water.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Cyanazine in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/60).

12.33 Cyanide

Cyanides can be found in some foods, particularly in some developing countries, and they are occasionally found in drinking-water, primarily as a consequence of industrial contamination.

Guideline value	0.07 mg/litre
Occurrence	Occasionally found in drinking-water
TDI	12 µg/kg of body weight, based on a LOAEL of 1.2 mg/kg of body weight per day for effects on behavioural patterns and serum biochemistry in a 6-month study in pigs, using an uncertainty factor of 100 for inter- and intraspecies variation (no additional factor for use of a LOAEL instead of a NOAEL was considered necessary because of doubts over the biological significance of the observed changes)
Limit of detection	2 µg/litre by titrimetric and photometric techniques
Treatment achievability	Cyanide is removed from water by high doses of chlorine.
Guideline derivation	
• allocation to water	20% of TDI (because exposure to cyanide from other sources is normally small and because exposure from water is only intermittent)
• weight	60-kg adult
• consumption	2 litres/day
Additional considerations	The guideline value is considered to be protective for acute and long-term exposure.

Toxicological review

The acute toxicity of cyanides is high. Effects on the thyroid and particularly the nervous system were observed in some populations as a consequence of the long-term consumption of inadequately processed cassava containing high levels of cyanide.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* recommended a maximum allowable concentration of 0.01 mg/litre for cyanide, based on health concerns. This value was raised to 0.2 mg/litre in the 1963 International Standards. The tentative upper concentration limit was lowered to 0.05 mg/litre in the 1971 International Standards upon consideration of the ADI of hydrogen cyanide residues in some fumigated foods of 0.05 mg/kg of body weight and to ensure that the water source is not too highly contaminated by industrial effluents and that water treatment has been adequate. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was determined that a guideline value of 0.1 mg/litre would be a reasonable level for the protection of public health. A health-based guideline value of 0.07 mg/litre, which was considered to be protective for both acute and long-term exposure, was derived in the 1993 Guidelines.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Cyanide in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/5).

12.34 Cyanogen chloride

Cyanogen chloride is a by-product of chloramination. It is a reaction product of organic precursors with hypochlorous acid in the presence of ammonium ion. Concentrations detected in drinking-water treated with chlorine and chloramine were 0.4 and 1.6 µg/litre, respectively.

Cyanogen chloride is rapidly metabolized to cyanide in the body. There are few data on the oral toxicity of cyanogen chloride, and the guideline value is based, therefore, on cyanide. The guideline value is 70 µg/litre for cyanide as total cyanogenic compounds (see Cyanide in section 12.33).

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to cyanogen chloride. The 1993 Guidelines derived a health-based guideline value for cyanogen chloride based on cyanide, as cyanogen chloride is rapidly metabolized to cyanide in the body and as there are few data on the oral toxicity of cyanogen chloride. The guideline value is 0.07 mg/litre for cyanide as total cyanogenic compounds (see Cyanide in section 12.33).

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Cyanogen chloride in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/51).

12.35 2,4-D (2,4-dichlorophenoxyacetic acid)

The term 2,4-D is used here to refer to the free acid, 2,4-dichlorophenoxyacetic acid (CAS No. 94-75-7). Commercial 2,4-D products are marketed as the free acid, alkali

and amine salts, and ester formulations. 2,4-D itself is chemically stable, but its esters are rapidly hydrolysed to the free acid. 2,4-D is a systemic herbicide used for control of broad-leaved weeds, including aquatic weeds. 2,4-D is rapidly biodegraded in the environment. Residues of 2,4-D in food rarely exceed a few tens of micrograms per kilogram.

Guideline value	0.03 mg/litre
Occurrence	Levels in water usually below 0.5 µg/litre, although concentrations as high as 30 µg/litre have been measured
ADI	0.01 mg/kg of body weight for the sum of 2,4-D and its salts and esters, expressed as 2,4-D, on the basis of a NOAEL of 1 mg/kg of body weight per day in a 1-year study of toxicity in dogs (for a variety of effects, including histopathological lesions in kidneys and liver) and a 2-year study of toxicity and carcinogenicity in rats (for renal lesions)
Limit of detection	0.1 µg/litre by gas–liquid chromatography with electrolytic conductivity detection
Treatment achievability	1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of ADI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	The guideline value applies to 2,4-D, as salts and esters of 2,4-D are rapidly hydrolysed to the free acid in water

Toxicological review

Epidemiological studies have suggested an association between exposure to chlorophenoxy herbicides, including 2,4-D, and two forms of cancer in humans: soft-tissue sarcomas and non-Hodgkin lymphoma. The results of these studies, however, are inconsistent; the associations found are weak, and conflicting conclusions have been reached by the investigators. Most of the studies did not provide information on exposure specifically to 2,4-D, and the risk was related to the general category of chlorophenoxy herbicides, a group that includes 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), which was potentially contaminated with dioxins. JMPR concluded that it was not possible to evaluate the carcinogenic potential of 2,4-D on the basis of the available epidemiological studies. JMPR has also concluded that 2,4-D and its salts and esters are not genotoxic. The toxicity of the salts and esters of 2,4-D is comparable to that of the acid.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to 2,4-D, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guide-*

lines for Drinking-water Quality, published in 1984, a health-based guideline value of 0.1 mg/litre was recommended for 2,4-D, based on the ADI recommended by WHO in 1976, but it was noted that some individuals may be able to detect 2,4-D by taste and odour at levels exceeding 0.05 mg/litre. The 1993 Guidelines established a health-based guideline value of 0.03 mg/litre for 2,4-D in drinking-water. This guideline value was retained in the addendum to these Guidelines, published in 1998, but was based on the more recent (1996) toxicological evaluation conducted by JMPR. This guideline value applies to 2,4-D, as salts and esters of 2,4-D are rapidly hydrolysed to the free acid in water.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal references

FAO/WHO (1997) *Pesticide residues in food – 1996. Evaluations 1996. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/97.1).

WHO (2003) *2,4-D in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/70).

12.36 2,4-DB

The half-lives for degradation of chlorophenoxy herbicides, including 2,4-DB (CAS No. 94-82-6), in the environment are in the order of several days. Chlorophenoxy herbicides are not often found in food.

Guideline value	0.09 mg/litre
Occurrence	Chlorophenoxy herbicides not frequently found in drinking- water; when detected, concentrations are usually no greater than a few micrograms per litre
TDI	30 µg/kg of body weight, based on a NOAEL of 3 mg/kg of body weight per day for effects on body and organ weights, blood chemistry and haematological parameters in a 2-year study in rats, with an uncertainty factor of 100 (for inter- and intraspecies variation)
Limit of detection	1 µg/litre to 1 mg/litre for various methods commonly used for the determination of chlorophenoxy herbicides in water, including solvent extraction, separation by GC, gas-liquid chromatography, thin-layer chromatography or HPLC, with ECD or UV detection
Treatment achievability	0.1 µg/litre should be achievable using GAC

Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional considerations	The NOAEL used in the guideline value derivation is similar to the NOAEL of 2.5 mg/kg of body weight per day obtained in a short-term study in beagle dogs and the NOAEL for hepatocyte hypertrophy of 5 mg/kg of body weight per day obtained in a 3-month study in rats.

Toxicological review

Chlorophenoxy herbicides, as a group, have been classified in Group 2B by IARC. However, the available data from studies in exposed populations and animals do not permit assessment of the carcinogenic potential to humans of any specific chlorophenoxy herbicide. Therefore, drinking-water guidelines for these compounds are based on a threshold approach for other toxic effects.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to chlorophenoxy herbicides, including 2,4-DB, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. 2,4-DB was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 *Guidelines* established a health-based guideline value of 0.09 mg/litre for 2,4-DB.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/44).

12.37 DDT and metabolites

The structure of DDT (CAS No. 107917-42-0) permits several different isomeric forms, and commercial products consist predominantly of *p,p'*-DDT. Its use has been restricted or banned in several countries, although DDT is still used in some countries for the control of vectors that transmit yellow fever, sleeping sickness, typhus, malaria and other insect-transmitted diseases. DDT and its metabolites are persistent

in the environment and resistant to complete degradation by microorganisms. Food is the major source of intake of DDT and related compounds for the general population.

Guideline value	0.001 mg/litre
Occurrence	Detected in surface water at concentrations below 1 µg/litre; also detected in drinking-water at 100-fold lower concentrations
PTDI	0.01 mg/kg of body weight based on a NOAEL of 1 mg/kg of body weight per day for developmental toxicity in rats, applying an uncertainty factor of 100
Limit of detection	0.011 µg/litre by GC using an ECD
Treatment achievability	0.1 µg/litre should be achievable using coagulation or GAC
Guideline derivation	
● allocation to water	1% of PTDI
● weight	10-kg child
● consumption	1 litre/day
Additional comments	<ul style="list-style-type: none"> ● DDT is listed under the Stockholm Convention on Persistent Organic Pollutants. Hence, monitoring may occur in addition to that required by drinking-water guidelines. ● The guideline value is derived on the basis of a 10-kg child consuming 1 litre of drinking-water per day, because infants and children may be exposed to greater amounts of chemicals in relation to their body weight and because of concern over the bioaccumulation of DDT. ● It should be emphasized that the benefits of DDT use in malaria and other vector control programmes outweigh any health risk from the presence of DDT in drinking-water.

Toxicological review

A working group convened by IARC classified the DDT complex as a non-genotoxic carcinogen in rodents and a potent promoter of liver tumours. IARC has concluded that there is insufficient evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of DDT (Group 2B) based upon liver tumours observed in rats and mice. The results of epidemiological studies of pancreatic cancer, multiple myeloma, non-Hodgkin lymphoma and uterine cancer did not support the hypothesis of an association with environmental exposure to the DDT complex. Conflicting data were obtained with regard to some genotoxic end-points. In most studies, DDT did not induce genotoxic effects in rodent or human cell systems, nor was it mutagenic to fungi or bacteria. The US Agency for Toxic Substances and Disease Registry concluded that the DDT complex could impair reproduction and/or development in several species. Hepatic effects of DDT in rats include increased liver weights, hypertrophy, hyperplasia, induction of microsomal enzymes, including cytochrome P450, cell necrosis, increased activity of serum liver enzymes and mitogenic effects, which might be related to a regenerative liver response to DDT.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to DDT, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.001 mg/litre was recommended for DDT (total isomers), based on the ADI recommended by JMPR in 1969. The 1993 Guidelines established a health-based guideline value of 0.002 mg/litre for DDT and its metabolites in drinking-water, derived from the ADI recommended by JMPR in 1984 and taking into consideration the fact that infants and children may be exposed to greater amounts of chemicals in relation to their body weight, concern over the bioaccumulation of DDT and the significant exposure to DDT by routes other than water. It was noted that the guideline value exceeds the water solubility of DDT of 0.001 mg/litre, but that some DDT may be adsorbed onto the small amount of particulate matter present in drinking-water, so the guideline value could be reached under certain circumstances. It was also emphasized that the benefits of DDT use in malaria and other vector control programmes far outweigh any health risk from the presence of DDT in drinking-water.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (2001) *Pesticide residues in food – 2000. Evaluations – 2000. Part II – Toxicology*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/01.3).

WHO (2003) *DDT and its derivatives in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/89).

12.38 Dialkyltins

The group of chemicals known as the organotins is composed of a large number of compounds with differing properties and applications. The most widely used of the organotins are the disubstituted compounds, which are employed as stabilizers in plastics, including polyvinyl chloride (PVC) water pipes, and the trisubstituted compounds, which are widely used as biocides.

The disubstituted compounds that may leach from PVC water pipes at low concentrations for a short time after installation are primarily immunotoxins, although they appear to be of low general toxicity. The data available are insufficient to permit the proposal of guideline values for individual dialkyltins.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to dialkyltins. The 1993 Guidelines concluded that the data available were insufficient to permit the proposal of guideline values for individual dialkyltins.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Dialkyltins in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/109).

12.39 1,2-Dibromo-3-chloropropane (DBCP)

1,2-Dibromo-3-chloropropane (CAS No. 96-12-8) is a soil fumigant that is highly soluble in water. It has a taste and odour threshold in water of 10 µg/litre. DBCP was detected in vegetables grown in treated soils, and low levels have been detected in air.

Guideline value	0.001 mg/litre
Occurrence	Limited survey found levels of up to a few micrograms per litre in drinking-water
Basis of guideline derivation	Linearized multistage model was applied to the data on the incidence of stomach, kidney and liver tumours in the male rat in a 104-week dietary study
Limit of detection	0.02 µg/litre by GC with ECD
Treatment achievability	1 µg/litre should be achievable using air stripping followed by GAC
Additional comments	The guideline value of 1 µg/litre should be protective for the reproductive toxicity of DBCP.

Toxicological review

On the basis of animal data from different strains of rats and mice, DBCP was determined to be carcinogenic in both sexes by the oral, inhalation and dermal routes. DBCP was also determined to be a reproductive toxicant in humans and several species of laboratory animals. DBCP was found to be genotoxic in a majority of *in vitro* and *in vivo* assays. IARC has classified DBCP in Group 2B based upon sufficient evidence of carcinogenicity in animals. Recent epidemiological evidence suggests an increase in cancer mortality in individuals exposed to high levels of DBCP.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to DBCP, but the 1971 *International Standards* suggested that pesticide residues that may

occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. DBCP was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines calculated a guideline value of 0.001 mg/litre for DBCP in drinking-water, corresponding to an upper-bound excess lifetime cancer risk of 10^{-5} and sufficiently protective for the reproductive toxicity of the pesticide. It was noted that for a contaminated water supply, extensive treatment would be required to reduce the level of DBCP to the guideline value.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *1,2-Dibromo-3-chloropropane in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/34).

12.40 1,2-Dibromoethane (ethylene dibromide)

1,2-Dibromoethane (CAS No. 106-93-4) is used as a lead scavenger in tetra-alkyl lead petrol and antiknock preparations and as a fumigant for soils, grains and fruits. However, with the phasing out of leaded petrol and of the use of 1,2-dibromoethane in agricultural applications in many countries, use of this substance has declined significantly. In addition to its continued use as a petrol additive in some countries, 1,2-dibromoethane is currently used principally as a solvent and as an intermediate in the chemical industry.

Provisional guideline value	0.0004 mg/litre (0.4 µg/litre) The guideline value is provisional due to serious limitations of the critical studies.
Occurrence	Detected in groundwater following its use as a soil fumigant at concentrations as high as 100 µg/litre
Basis of guideline derivation	Lower end of the range (and thus more conservative estimate) of lifetime low-dose cancer risks calculated by linearized multistage modelling of the incidences of haemangiosarcomas and tumours in the stomach, liver, lung and adrenal cortex (adjusted for the observed high early mortality, where appropriate, and corrected for the expected rate of increase in tumour formation in rodents in a standard bioassay of 104 weeks) of rats and/or mice exposed to 1,2-dibromoethane by gavage

Limit of detection	0.01 µg/litre by microextraction GC/MS; 0.03 µg/litre by purge and trap GC with halogen-specific detector; 0.8 µg/litre by purge-and-trap capillary column GC with photoionization and electrolytic conductivity detectors in series
Treatment achievability	0.1 µg/litre should be achievable using GAC

Toxicological review

1,2-Dibromoethane has induced an increased incidence of tumours at several sites in all carcinogenicity bioassays identified in which rats or mice were exposed to the compound by gavage, ingestion in drinking-water, dermal application and inhalation. However, many of these studies were characterized by high early mortality, limited histopathological examination, small group sizes or use of only one exposure level. The substance acted as an initiator of liver foci in an initiation/promotion assay but did not initiate skin tumour development. 1,2-Dibromoethane was consistently genotoxic in *in vitro* assays, although results of *in vivo* assays were mixed. Biotransformation to active metabolites, which have been demonstrated to bind to DNA, is probably involved in the induction of tumours. Available data do not support the existence of a non-genotoxic mechanism of tumour induction. The available data thus indicate that 1,2-dibromoethane is a genotoxic carcinogen in rodents. Data on the potential carcinogenicity in humans are inadequate; however, it is likely that 1,2-dibromoethane is metabolized similarly in rodent species and in humans (although there may be varying potential for the production of active metabolites in humans, owing to genetic polymorphism). IARC classified 1,2-dibromoethane in Group 2A (the agent is probably carcinogenic to humans).

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to 1,2-dibromoethane, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. 1,2-Dibromoethane was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 *Guidelines* noted that 1,2-dibromoethane appears to be a genotoxic carcinogen. However, as the studies to date were inadequate for mathematical risk extrapolation, a guideline value for 1,2-dibromoethane was not derived. The *Guidelines* recommended that 1,2-dibromoethane be re-evaluated as soon as new data became available. In the addendum to these *Guidelines*, published in 1998, the guideline value that corresponds to an upper-bound excess lifetime cancer risk for various tumour types of 10^{-5} was calculated to be in the range 0.0004–0.015 mg/litre. This guideline value was considered to be provisional because of the serious limitations of the critical studies.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- IPCS (1995) *Report of the 1994 meeting of the Core Assessment Group*. Geneva, World Health Organization, International Programme on Chemical Safety, Joint Meeting on Pesticides (WHO/PCS/95.7).
- IPCS (1996) *1,2-Dibromoethane*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 177).
- WHO (2003) *1,2-Dibromoethane in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/66).

12.41 Dichloroacetic acid

Chlorinated acetic acids, including dichloroacetic acid (DCA), are formed from organic material during water chlorination. DCA has been used as a therapeutic agent to treat lactic acidosis, diabetes and familial hyperlipidaemia in humans.

Provisional guideline value	0.05 mg/litre The guideline value is designated as provisional because the data on treatment are insufficient to ensure that the health-based value of 0.04 mg/litre is technically achievable in a wide range of circumstances. Difficulties in meeting a guideline value must never be a reason to compromise adequate disinfection.
Occurrence	Found in groundwater and surface water distribution systems at concentrations up to about 100 µg/litre, with mean concentrations below 20 µg/litre
Basis of guideline derivation	Using the tumour prevalence data from male mice, the combined data for carcinomas and adenomas in male B6C3F1 mice exposed to doses of 0, 8, 84, 168, 315 or 429 mg/kg of body weight per day for up to 2 years were plotted using the US EPA's Benchmark Dose software version 1.3.1. The slope factor of 0.0075 (mg/kg of body weight per day) ⁻¹ was derived from the BMDL ₁₀ using a linear multistage model of the dose-response data.
Limit of detection	<0.1–0.4 µg/litre by GC with ECD; practical quantification level 1 µg/litre
Treatment achievability	Concentrations may be reduced by installing or optimizing coagulation to remove precursors and/or by controlling the pH during chlorination.
Additional comments	The concentration associated with a 10 ⁻⁵ upper-bound excess lifetime cancer risk is 40 µg/litre. However, it may not be possible to adequately disinfect potable water and maintain DCA levels below 40 µg/litre, so the provisional guideline value of 50 µg/litre is retained.

Toxicological review

IARC reclassified DCA as Group 2B (possibly carcinogenic to humans) in 2002, based on the absence of data on human carcinogenicity and sufficient evidence of its carcinogenicity in experimental animals. This classification was based primarily on findings of liver tumours in rats and mice. Genotoxicity data are considered to be inconclusive, particularly at lower doses. Glycogen deposition, peroxisome proliferation, changes in signal transduction pathways and DNA hypomethylation have all been observed following DCA exposure and have been hypothesized to be involved in its carcinogenicity. However, the available data are not sufficient to establish a cancer mode of action with reasonable certainty, especially at the very low exposure levels expected to apply to humans ingesting chlorinated drinking-water. Recent data suggest that there may be more than one mechanism leading to tumours, since altered hepatic foci from treated mice were found to have three different types of cellular characteristics.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to DCA. In the 1993 Guidelines, a provisional guideline value of 0.05 mg/litre was derived for DCA; the guideline value was designated as provisional because the data were insufficient to ensure that the value was technically achievable. This guideline value was brought forward to the third edition.

Assessment date

The risk assessment was conducted in 2004.

Principal reference

WHO (2005) *Dichloroacetic acid in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/121).

12.42 Dichlorobenzenes (1,2-dichlorobenzene, 1,3-dichlorobenzene, 1,4-dichlorobenzene)

The dichlorobenzenes (DCBs) are widely used in industry and in domestic products such as odour-masking agents, chemical dyestuffs and pesticides. Sources of human exposure are predominantly air and food.

Guideline values

1,2-Dichlorobenzene	1 mg/litre
1,4-Dichlorobenzene	0.3 mg/litre

GUIDELINES FOR DRINKING-WATER QUALITY

Occurrence	Have been found in raw water sources at levels as high as 10 µg/litre and in drinking-water at concentrations up to 3 µg/litre; much higher concentrations (up to 7 mg/litre) present in contaminated groundwater
TDIs	
1,2-Dichlorobenzene	429 µg/kg of body weight, based on a NOAEL of 60 mg/kg of body weight per day for tubular degeneration of the kidney identified in a 2-year mouse gavage study, correcting for 5 days per week dosing and using an uncertainty factor of 100 (for inter- and intraspecies variation)
1,4-Dichlorobenzene	107 µg/kg of body weight, based on a LOAEL of 150 mg/kg of body weight per day for kidney effects identified in a 2-year rat study, correcting for 5 days per week dosing and using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the use of a LOAEL instead of a NOAEL and the carcinogenicity end-point)

12. CHEMICAL FACT SHEETS

Limit of detection	0.01–0.25 µg/litre by gas–liquid chromatography with ECD; 3.5 µg/litre by GC using a photoionization detector
Treatment achievability	0.01 mg/litre should be achievable using air stripping
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	Guideline values for both 1,2- and 1,4-DCB far exceed their lowest reported taste thresholds in water of 1 and 6 µg/litre, respectively.

Toxicological review

1,2-Dichlorobenzene

1,2-DCB is of low acute toxicity by the oral route of exposure. Oral exposure to high doses of 1,2-DCB affects mainly the liver and kidneys. The balance of evidence suggests that 1,2-DCB is not genotoxic, and there is no evidence for its carcinogenicity in rodents.

1,3-Dichlorobenzene

There are insufficient toxicological data on this compound to permit a guideline value to be proposed, but it should be noted that it is rarely found in drinking-water.

1,4-Dichlorobenzene

1,4-DCB is of low acute toxicity, but there is evidence that it increases the incidence of renal tumours in rats and of hepatocellular adenomas and carcinomas in mice after long-term exposure. IARC has placed 1,4-DCB in Group 2B. 1,4-DCB is not considered to be genotoxic, and the relevance for humans of the tumours observed in animals is doubtful.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to DCBs. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline value was recommended for 1,2- or 1,4-DCB after a detailed evaluation of the compounds. Toxicological limits for drinking-water of 0.005–0.05 mg/litre were derived based on an ADI; given that the threshold odour concentrations are 0.003 mg/litre for 1,2-DCB and 0.001 mg/litre for 1,4-DCB, 10% of each of these values was recommended as a level unlikely to give rise to taste and odour problems in drinking-water supplies. The 1993 Guidelines calculated a health-based guideline value of 1 mg/litre for 1,2-DCB, which far exceeds the lowest reported taste threshold of 1,2-DCB in water (0.001 mg/litre). There were insufficient toxicological data on 1,3-DCB to permit a guideline value to be proposed, but the 1993 Guidelines noted that it is rarely found in drinking-water. A health-based guideline value of 0.3 mg/litre was proposed for 1,4-DCB, which far exceeds the lowest reported odour threshold of 1,4-DCB in water (0.0003 mg/litre).

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Dichlorobenzenes in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/28).

12.43 1,1-Dichloroethane

1,1-Dichloroethane is used as a chemical intermediate and solvent. There are limited data showing that it can be present at concentrations of up to 10 µg/litre in drinking-water. However, because of the widespread use and disposal of this chemical, its occurrence in groundwater may increase.

1,1-Dichloroethane is rapidly metabolized by mammals to acetic acid and a variety of chlorinated compounds. It is of relatively low acute toxicity, and limited data are available on its toxicity from short- and long-term studies. There is limited *in vitro* evidence of genotoxicity. One carcinogenicity study by gavage in mice and rats provided no conclusive evidence of carcinogenicity, although there was some evidence of an increased incidence of haemangiosarcomas in treated animals.

In view of the very limited database on toxicity and carcinogenicity, it was concluded that no guideline value should be proposed.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to 1,1-dichloroethane. In view of the very limited database on toxicity and carcinogenicity, the 1993 Guidelines concluded that no guideline value for 1,1-dichloroethane should be proposed.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *1,1-Dichloroethane in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/19).

12.44 1,2-Dichloroethane

1,2-Dichloroethane is used mainly as an intermediate in the production of vinyl chloride and other chemicals and to a lesser extent as a solvent. It may enter surface waters via effluents from industries that manufacture or use the substance. It may also enter groundwater, where it may persist for long periods, following disposal in waste sites. It is found in urban air.

Guideline value	0.030 mg/litre
Occurrence	Has been found in drinking-water at levels of up to a few micrograms per litre
Basis of guideline derivation	Applying the linearized multistage model to haemangiosarcomas observed in male rats in a 78-week gavage study
Limit of detection	0.06–2.8 µg/litre by GC/MS; 0.03–0.2 µg/litre by GC with electrolytic conductivity detector; 5 µg/litre by GC with FID; 0.03 µg/litre by GC with photoionization detection
Treatment achievability	0.0001 mg/litre should be achievable using GAC
Additional considerations	The guideline value of 0.030 mg/litre is consistent with the value derived from IPCS (1998), based on a 10^{-5} risk level.

Toxicological review

IARC has classified 1,2-dichloroethane in Group 2B (possible human carcinogen). It has been shown to produce statistically significant increases in a number of tumour types in laboratory animals, including the relatively rare haemangiosarcoma, and the balance of evidence indicates that it is potentially genotoxic. Targets of 1,2-dichloroethane toxicity in orally exposed animals included the immune system, central nervous system, liver and kidney. Data indicate that 1,2-dichloroethane is less potent when inhaled.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to 1,2-dichloroethane. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.01 mg/litre was recommended for 1,2-dichloroethane, while noting that the mathematical model appropriate to chemical carcinogens that was used in its derivation involved considerable uncertainty. The 1993 Guidelines calculated a guideline value of 0.03 mg/litre for 1,2-dichloroethane on the basis of haemangiosarcomas observed in male rats, corresponding to an upper-bound excess lifetime cancer risk of 10^{-5} .

Assessment date

The risk assessment was conducted in 2003.

Principal references

- IPCS (1995) *1,2-Dichloroethane*, 2nd ed. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 176).
- IPCS (1998) *1,2-Dichloroethane*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 1).
- WHO (2003) *1,2-Dichloroethane in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/67).

12.45 1,1-Dichloroethene

1,1-Dichloroethene, or vinylidene chloride, is used mainly as a monomer in the production of polyvinylidene chloride co-polymers and as an intermediate in the synthesis of other organic chemicals. It is an occasional contaminant of drinking-water, usually being found together with other chlorinated hydrocarbons. There are no data on levels in food, but levels in air are generally less than 40 ng/m³ except at some manufacturing sites. 1,1-Dichloroethene is detected in finished drinking-water taken from groundwater sources at median concentrations of 0.28–1.2 µg/litre and in public drinking-water supplies at concentrations ranging from ≤0.2 to 0.5 µg/litre.

1,1-Dichloroethene is a central nervous system depressant and may cause liver and kidney toxicity in occupationally exposed humans. It causes liver and kidney damage in laboratory animals. IARC has placed 1,1-dichloroethene in Group 3. It was found to be genotoxic in a number of test systems *in vitro* but was not active in the dominant lethal and micronucleus assays *in vivo*. It induced kidney tumours in mice in one inhalation study but was reported not to be carcinogenic in a number of other studies, including several in which it was given in drinking-water.

A health-based value of 140 µg/litre (rounded value) can be derived from a TDI of 0.046 mg/kg of body weight, derived using the BMD approach from a study in which the critical effect was minimal hepatocellular mid-zonal fatty change in female rats. However, this value is significantly higher than the concentrations of 1,1-dichloroethene normally found in drinking-water. It is therefore considered unnecessary to set a formal guideline value for 1,1-dichloroethene in drinking-water.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to 1,1-dichloroethene. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.0003 mg/litre was recommended for 1,1-dichloroethene, while noting that the mathematical model appropriate to chemical carcinogens that was used in its derivation involved considerable uncertainty. A health-based guideline value of 0.03 mg/litre for 1,1-dichloroethene was recommended in the 1993 Guidelines. This value was brought forward to the third edition of the Guidelines.

Assessment date

The risk assessment was conducted in 2004.

Principal references

- IPCS (2003) *1,1-Dichloroethene (vinylidene chloride)*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 51).
- WHO (2005) *1,1-Dichloroethene in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/20).

12.46 1,2-Dichloroethene

1,2-Dichloroethene exists in a *cis* and a *trans* form. The *cis* form is more frequently found as a water contaminant. The presence of these two isomers, which are metabolites of other unsaturated halogenated hydrocarbons in wastewater and anaerobic groundwater, may indicate the simultaneous presence of more toxic organochlorine chemicals, such as vinyl chloride. Accordingly, their presence indicates that more intensive monitoring should be conducted. There are no data on exposure from food. Concentrations in air are low, with higher concentrations, in the microgram per cubic metre range, near production sites. The *cis* isomer was previously used as an anaesthetic.

Guideline value	0.05 mg/litre
Occurrence	Has been found in drinking-water supplies derived from groundwater at levels up to 120 µg/litre
TDI	17 µg/kg of body weight, based on a NOAEL (for increases in serum alkaline phosphatase levels and increased thymus weight) of 17 mg/kg of body weight from a 90-day study in mice administered <i>trans</i> -1,2-dichloroethene in drinking-water, using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the short duration of the study)
Limit of detection	0.17 µg/litre by GC with MS
Treatment achievability	0.01 mg/litre should be achievable using GAC or air stripping

Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	Data on the <i>trans</i> isomer were used to calculate a joint guideline value for both isomers because toxicity for the <i>trans</i> isomer occurred at a lower dose than for the <i>cis</i> isomer and because data suggest that the mouse is a more sensitive species than the rat.

Toxicological review

There is little information on the absorption, distribution and excretion of 1,2-dichloroethene. However, by analogy with 1,1-dichloroethene, it would be expected to be readily absorbed, distributed mainly to the liver, kidneys and lungs and rapidly excreted. The *cis* isomer is more rapidly metabolized than the *trans* isomer in *in vitro* systems. Both isomers have been reported to cause increased serum alkaline phosphatase levels in rodents. In a 3-month study in mice given the *trans* isomer in drinking-water, there was a reported increase in serum alkaline phosphatase and reduced thymus and lung weights. Transient immunological effects were also reported, the toxicological significance of which is unclear. *Trans*-1,2-dichloroethene also caused reduced kidney weights in rats, but at higher doses. Only one rat toxicity study is available for the *cis* isomer, which produced toxic effects in rats similar in magnitude to those induced by the *trans* isomer in mice, but at higher doses. There are limited data to suggest that both isomers may possess some genotoxic activity. There is no information on carcinogenicity.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to 1,2-dichloroethene. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline value was recommended after a detailed evaluation of the compound. In the 1993 Guidelines, a joint guideline value of 0.05 mg/litre was calculated for both 1,2-dichloroethene isomers using toxicity data on the *trans* isomer.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *1,2-Dichloroethene in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/72).

12.47 Dichloromethane

Dichloromethane, or methylene chloride, is widely used as a solvent for many purposes, including coffee decaffeination and paint stripping. Exposure from drinking-water is likely to be insignificant compared with that from other sources.

Guideline value	0.02 mg/litre
Occurrence	Dichloromethane has been found in surface water samples at concentrations ranging from 0.1 to 743 µg/litre. Levels are usually higher in groundwater because volatilization is restricted; concentrations as high as 3600 µg/litre have been reported. Mean concentrations in drinking-water were less than 1 µg/litre.
TDI	6 µg/kg of body weight, derived from a NOAEL of 6 mg/kg of body weight per day for hepatotoxic effects in a 2-year drinking-water study in rats, using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for concern about carcinogenic potential)
Limit of detection	0.3 µg/litre by purge-and-trap GC with MS detection (note that dichloromethane vapour readily penetrates tubing during the procedure)
Treatment achievability	20 µg/litre should be achievable using air stripping
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

Dichloromethane is of low acute toxicity. An inhalation study in mice provided conclusive evidence of carcinogenicity, whereas drinking-water studies in rats and mice provided only suggestive evidence. IARC has placed dichloromethane in Group 2B; however, the balance of evidence suggests that it is not a genotoxic carcinogen and that genotoxic metabolites are not formed in relevant amounts *in vivo*.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to dichloromethane. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline value was recommended after a detailed evaluation of the compound. The 1993 Guidelines established a health-based guideline value of 0.02 mg/litre for dichloromethane, noting that widespread exposure from other sources is possible.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Dichloromethane in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/18).

12.48 1,2-Dichloropropane (1,2-DCP)

1,2-Dichloropropane (CAS No. 78-87-5) is used as an insecticide fumigant on grain and soil and to control peach tree borers. It is also used as an intermediate in the production of perchloroethylene and other chlorinated products and as a solvent. 1,2-DCP is relatively resistant to hydrolysis, is poorly adsorbed onto soil and can migrate into groundwater.

Provisional guideline value	0.04 mg/litre The guideline value is provisional owing to limitations of the toxicological database.
Occurrence	Detected in groundwater and drinking-water, usually at concentrations below 20 µg/litre, although levels as high as 440 µg/litre have been measured in well water
TDI	14 µg/kg of body weight based on a LOAEL of 71.4 mg/kg of body weight per day (100 mg/kg of body weight per day corrected for 5 days per week dosing) for changes in haematological parameters in a 13-week study in male rats, with an uncertainty factor of 5000 (100 for inter- and intraspecies variation, 10 for use of a LOAEL and 5 to reflect limitations of the database, including the limited data on <i>in vivo</i> genotoxicity and use of a subchronic study)
Limit of detection	0.02 µg/litre by a purge-and-trap GC method with an electrolytic conductivity detector or GC/MS
Treatment achievability	1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

1,2-DCP was evaluated by IARC in 1986 and 1987. The substance was classified in Group 3 (not classifiable as to its carcinogenicity to humans) on the basis of limited evidence for its carcinogenicity in experimental animals and insufficient data with which to evaluate its carcinogenicity in humans. Results from *in vitro* assays for mutagenicity were mixed. The *in vivo* studies, which were limited in number and design, were negative. In accordance with the IARC evaluation, the evidence from the long-term carcinogenicity studies in mice and rats was considered limited, and it was concluded that the use of a threshold approach for the toxicological evaluation of 1,2-DCP was appropriate.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to 1,2-DCP, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. 1,2-DCP was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines proposed a provisional health-based guideline value of 0.02 mg/litre for 1,2-DCP in drinking-water. The value was provisional because an uncertainty factor of 10 000 was used in its derivation. This guideline value was amended to 0.04 mg/litre in the addendum to these Guidelines, published in 1998, using a lower uncertainty factor. This guideline value was considered to be provisional owing to the magnitude of the uncertainty factor and the fact that the database had not changed since the previous guideline value had been derived.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *1,2-Dichloropropane (1,2-DCP) in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/61).

12.49 1,3-Dichloropropane

1,3-Dichloropropane (CAS No. 142-28-9) has several industrial uses and may be found as a contaminant of soil fumigants containing 1,3-dichloropropene. It is rarely found in water.

1,3-Dichloropropane is of low acute toxicity. There is some indication that it may be genotoxic in bacterial systems. No short-term, long-term, reproductive or developmental toxicity data pertinent to exposure via drinking-water could be located in the literature. The available data are considered insufficient to permit recommendation of a guideline value.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to 1,3-dichloropropane, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. 1,3-Dichloropropane was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines concluded that the available data

were insufficient to permit recommendation of a guideline value for 1,3-dichloropropane in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *1,3-Dichloropropane in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/35).

12.50 1,3-Dichloropropene

1,3-Dichloropropene (CAS Nos. 542-75-6 isomer mixture; 10061-01-5 *cis* isomer; 10061-02-6 *trans* isomer) is a soil fumigant, the commercial product being a mixture of *cis* and *trans* isomers. It is used to control a wide variety of soil pests, particularly nematodes in sandy soils. Notwithstanding its high vapour pressure, it is soluble in water at the gram per litre level and can be considered a potential water contaminant.

Guideline value	0.02 mg/litre
Occurrence	Has been found in surface water and groundwater at concentrations of a few micrograms per litre
Basis of guideline derivation	Calculated by applying the linearized multistage model to the observation of lung and bladder tumours in female mice in a 2-year gavage study
Limit of detection	0.34 and 0.20 µg/litre by purge-and-trap packed column GC using an electrolytic conductivity detector or microcoulometric detector for <i>cis</i> -1,3-dichloropropene and <i>trans</i> -1,3-dichloropropene, respectively
Treatment achievability	No information found on removal from water

Toxicological review

1,3-Dichloropropene is a direct-acting mutagen that has been shown to produce forestomach tumours following long-term oral gavage exposure in rats and mice. Tumours have also been found in the bladder and lungs of female mice and the liver of male rats. Long-term inhalation studies in the rat have proved negative, whereas some benign lung tumours have been reported in inhalation studies in mice. IARC has classified 1,3-dichloropropene in Group 2B (possible human carcinogen).

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to 1,3-dichloropropene, but the 1971 *International Standards* suggested that pesticide

residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. 1,3-Dichloropropene was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines calculated a guideline value of 0.02 mg/litre for 1,3-dichloropropene in drinking-water, corresponding to an upper-bound excess lifetime cancer risk of 10^{-5} .

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *1,3-Dichloropropene in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/36).

12.51 Dichlorprop (2,4-DP)

The half-lives for degradation of chlorophenoxy herbicides, including dichlorprop (CAS No. 120-36-5), in the environment are in the order of several days. Chlorophenoxy herbicides are not often found in food.

Guideline value	0.1 mg/litre
Occurrence	Chlorophenoxy herbicides not frequently found in drinking-water; when detected, concentrations are usually no greater than a few micrograms per litre
TDI	36.4 µg/kg of body weight, based on a NOAEL for renal toxicity in a 2-year study in rats of 100 mg/kg of diet, equal to 3.64 mg/kg of body weight per day, applying an uncertainty factor of 100 (for intra- and interspecies variation)
Limit of detection	1 µg/litre to 1 mg/litre for various methods commonly used for the determination of chlorophenoxy herbicides in water, including solvent extraction, separation by GC, gas-liquid chromatography, thin-layer chromatography or HPLC, with ECD or UV detection
Treatment achievability	No data available
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

Chlorophenoxy herbicides, as a group, have been classified in Group 2B by IARC. However, the available data from studies in exposed populations and animals do not

permit assessment of the carcinogenic potential to humans of any specific chlorophenoxy herbicide. Therefore, drinking-water guidelines for these compounds are based on a threshold approach for other toxic effects. In dietary studies in rats, slight liver hypertrophy was observed in a 3-month study, and effects in a 2-year study included hepatocellular swelling, mild anaemia, increased incidence of brown pigment in the kidneys (possibly indicative of slight degeneration of the tubular epithelium) and decreased urinary specific gravity and protein.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to chlorophenoxy herbicides, including dichlorprop, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Dichlorprop was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 *Guidelines* established a health-based guideline value of 0.1 mg/litre for dichlorprop.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/44).

12.52 Di(2-ethylhexyl)adipate

Di(2-ethylhexyl)adipate (DEHA) is used mainly as a plasticizer for synthetic resins such as PVC. Reports of the presence of DEHA in surface water and drinking-water are scarce, but DEHA has occasionally been identified in drinking-water at levels of a few micrograms per litre. As a consequence of its use in PVC films, food is the most important source of human exposure (up to 20 mg/day).

DEHA is of low short-term toxicity; however, dietary levels above 6000 mg/kg of feed induce peroxisomal proliferation in the liver of rodents. This effect is often associated with the development of liver tumours. DEHA induced liver carcinomas in female mice at very high doses but not in male mice or rats. It is not genotoxic. IARC has placed DEHA in Group 3.

A health-based value of 80 µg/litre can be calculated for DEHA on the basis of a TDI of 280 µg/kg of body weight, based on fetotoxicity in rats, and allocating 1% of the TDI to drinking-water. However, because DEHA occurs at concentrations well

below those at which toxic effects are observed, it is not considered necessary to derive a health-based guideline value.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to DEHA. The 1993 Guidelines proposed a health-based guideline value of 0.08 mg/litre for DEHA in drinking-water.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Di(2-ethylhexyl)adipate in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/68).

12.53 Di(2-ethylhexyl)phthalate

Di(2-ethylhexyl)phthalate (DEHP) is used primarily as a plasticizer. Exposure among individuals may vary considerably because of the broad nature of products into which DEHP is incorporated. In general, food will be the main exposure route.

Guideline value	0.008 mg/litre
Occurrence	Found in surface water, groundwater and drinking-water in concentrations of a few micrograms per litre; in polluted surface water and groundwater, concentrations of hundreds of micrograms per litre have been reported
TDI	25 µg/kg of body weight, based on a NOAEL of 2.5 mg/kg of body weight per day for peroxisomal proliferation in the liver in rats, using an uncertainty factor of 100 for inter- and Intraspecies variation
Limit of detection	0.1 µg/litre by GC/MS
Treatment achievability	No data available
Guideline derivation	
• allocation to water	1% of TDI
• weight	60-kg adult
• consumption	2 litres/day
Additional comments	The reliability of some data on environmental water samples is questionable because of secondary contamination during sampling and working-up procedures. Concentrations that exceed the solubility more than 10-fold have been reported.

Toxicological review

In rats, DEHP is readily absorbed from the gastrointestinal tract. In primates (including humans), absorption after ingestion is lower. Species differences are also observed

in the metabolic profile. Most species excrete primarily the conjugated mono-ester in urine. Rats, however, predominantly excrete terminal oxidation products. DEHP is widely distributed in the body, with highest levels in liver and adipose tissue, without showing significant accumulation. The acute oral toxicity is low. The most striking effect in short-term toxicity studies is the proliferation of hepatic peroxisomes, indicated by increased peroxisomal enzyme activity and histopathological changes. The available information suggests that primates, including humans, are far less sensitive to this effect than rodents. In long-term oral carcinogenicity studies, hepatocellular carcinomas were found in rats and mice. IARC has concluded that DEHP is possibly carcinogenic to humans (Group 2B). In 1988, JECFA evaluated DEHP and recommended that human exposure to this compound in food be reduced to the lowest level attainable. The Committee considered that this might be achieved by using alternative plasticizers or alternatives to plastic material containing DEHP. In a variety of *in vitro* and *in vivo* studies, DEHP and its metabolites have shown no evidence of genotoxicity, with the exception of induction of aneuploidy and cell transformation.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to DEHP. The 1993 Guidelines established a health-based guideline value of 0.008 mg/litre for DEHP in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Di(2-ethylhexyl)phthalate in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/29).

12.54 Dimethoate

Dimethoate (CAS No. 60-51-5) is an organophosphorus insecticide used to control a broad range of insects in agriculture, as well as the housefly. It has a half-life of 18 h to 8 weeks and is not expected to persist in water, although it is relatively stable at pH 2–7. A total daily intake from food of 0.001 µg/kg of body weight has been estimated.

12. CHEMICAL FACT SHEETS

Guideline value	0.006 mg/litre
Occurrence	Detected at trace levels in a private well in Canada, but not detected in a Canadian survey of surface water or drinking- water supplies
ADI	0.002 mg/kg of body weight based on an apparent NOAEL of 1.2 mg/kg of body weight per day for reproductive performance in a study of reproductive toxicity in rats, applying an uncertainty factor of 500 to take into consideration concern regarding whether this could be a LOAEL
Limit of detection	0.05 µg/litre by GC/MS
Treatment achievability	1 µg/litre should be achievable using GAC and chlorination
Guideline derivation	
● allocation to water	10% of ADI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

In studies with human volunteers, dimethoate has been shown to be a cholinesterase inhibitor and a skin irritant. Dimethoate is not carcinogenic to rodents. JMPR concluded that although *in vitro* studies indicate that dimethoate has mutagenic potential, this potential does not appear to be expressed *in vivo*. In a multigeneration study of reproductive toxicity in rats, the NOAEL appeared to be 1.2 mg/kg of body weight per day, but there was some indication that reproductive performance may have been affected at lower doses. No data were available to assess whether the effects on reproductive performance were secondary to inhibition of cholinesterase. JMPR concluded that it was not appropriate to base the ADI on the results of the studies of volunteers, since the crucial end-point (reproductive performance) has not been assessed in humans. It was suggested that there may be a need to re-evaluate the toxicity of dimethoate after the periodic review of the residue and analytical aspects of dimethoate has been completed if it is determined that omethoate is a major residue.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to dimethoate, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Dimethoate was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (1997) *Pesticide residues in food – 1996 evaluations. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/97.1).

WHO (2003) *Dimethoate in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/90).

12.54(a) 1,4-Dioxane

1,4-Dioxane is used as a stabilizer in chlorinated solvents and as a solvent for resins, oils and waxes, for agricultural and biochemical intermediates and for adhesives, sealants, cosmetics, pharmaceuticals, rubber chemicals and surface coatings.

Guideline value	0.05 mg/litre (derived using TDI approach as well as linear multistage modelling)
Occurrence	Has been measured in surface water at concentrations up to 40 µg/litre and in groundwater at concentrations up to 80 µg/litre
TDI	16 µg/kg of body weight, based on a NOAEL of 16 mg/kg of body weight per day for hepatocellular tumours observed in a long-term drinking-water study in rats, using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for non-genotoxic carcinogenicity)
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Basis of guideline derivation based on carcinogenicity	Linear multistage model applied to data for hepatic tumours from drinking-water studies in rats
Limit of detection	0.1–50 µg/litre by GC/MS
Treatment achievability	Not removed using conventional water treatment processes; effectively removed by biological activated carbon treatment
Additional comments	Similar guideline values were derived using the TDI approach (assuming 1,4-dioxane is not genotoxic in humans at low doses) and linear multistage modelling (because the compound clearly induces multiple tumours in various organs).

Toxicological review

1,4-Dioxane caused hepatic and nasal cavity tumours in rodents in most long-term oral studies conducted. Tumours in peritoneum, skin and mammary gland were also observed in rats given a high dose. Lung tumours were specifically detected after intraperitoneal injection. Although cohort studies of workers did not reveal any elevation in the incidence of death by cancer, a significant increase in the incidence of liver cancer was found in a comparative mortality study. However, the evidence is inadequate for human carcinogenicity assessment because of small samples or lack of

exposure data. A possibly weak genotoxic potential of 1,4-dioxane has been suggested. IARC has classified 1,4-dioxane as Group 2B (possibly carcinogenic to humans).

History of guideline development

1,4-Dioxane was not referred to in the 1958, 1963 and 1971 WHO *International Standards for Drinking-water*, the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, the second edition of the Guidelines, published in 1993, or the third edition, published in 2004.

Assessment date

The risk assessment was conducted in 2004.

Principal reference

WHO (2005) *1,4-Dioxane in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/120).

12.55 Diquat

Diquat (CAS No. 2764-72-9) is a non-selective contact herbicide and crop desiccant. Diquat may also be used (at or below 1 mg/litre) as an aquatic herbicide for the control of free-floating and submerged aquatic weeds in ponds, lakes and irrigation ditches. Because of its rapid degradation in water and strong adsorption onto sediments, diquat has rarely been found in drinking-water.

Diquat does not appear to be carcinogenic or genotoxic. The main toxicological finding in experimental animals is cataract formation. A health-based value of 6 µg/litre for diquat ion can be calculated on the basis of an ADI of 0.002 mg of diquat ion per kg of body weight, based on cataract formation at the next higher dose in a 2-year study in rats. However, because diquat has rarely been found in drinking-water, it is not considered necessary to derive a guideline value. It should also be noted that the limit of detection of diquat in water is 0.001 mg/litre, and its practical quantification limit is about 0.01 mg/litre.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to diquat, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Diquat was not evaluated in the first two editions of the *Guidelines for Drinking-water Quality*, published in 1984 and 1993. In the addendum to the second edition of these Guidelines, published in 1998, a health-based value of 0.006 mg/litre was calculated for the diquat ion using the ADI established by JMPR in 1993. However, the limit of detection of diquat in water is 0.001 mg/litre, and its practical quantification limit is about 0.01 mg/litre.

A provisional guideline value of 0.01 mg/litre was therefore established for diquat.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (1994) *Pesticide residues in food – 1993. Evaluations – 1993. Part II – Toxicology*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/94.4).

WHO (2003) *Diquat in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/91).

12.56 Edetic acid (EDTA)

Human exposure to EDTA arises directly from its use in food additives, medicines, and personal care and hygiene products. Exposure to EDTA from drinking-water is probably very small in comparison with that from other sources. Once EDTA is present in the aquatic environment, its speciation will depend on the water quality and the presence of trace metals with which it will combine. The removal of EDTA from communal wastewater by biodegradation in sewage purification plants is very limited.

Guideline value	0.6 mg/litre (for EDTA as the free acid)
Occurrence	Present in surface waters generally at concentrations below 70 µg/litre, although higher concentrations (900 µg/litre) have been measured; detected in drinking-water prepared from surface waters at concentrations of 10–30 µg/litre
ADI	1.9 mg/kg of body weight as the free acid (ADI of 2.5 mg/kg of body weight proposed by JECFA for calcium disodium edetate as a food additive)
Limit of detection	1 µg/litre by potentiometric stripping analysis
Treatment achievability	0.01 mg/litre using GAC plus ozonation
Guideline derivation	
● allocation to water	1% of ADI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	Concern has been expressed over the ability of EDTA to complex, and therefore reduce the availability of, zinc. However, this is of significance only at elevated doses substantially in excess of those encountered in the environment.

Toxicological review

Calcium disodium edetate is poorly absorbed from the gut. The long-term toxicity of EDTA is complicated by its ability to chelate essential and toxic metals. Those toxicological studies that are available indicate that the apparent toxicological effects of EDTA have in fact been due to zinc deficiency as a consequence of complexation. EDTA does not appear to be teratogenic or carcinogenic in animals. The vast clinical experience of the use of EDTA in the treatment of metal poisoning has demonstrated its safety in humans.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not

refer to edetic acid. The 1993 Guidelines proposed a provisional health-based guideline value of 0.2 mg/litre for edetic acid, based on an ADI for calcium disodium edetate as a food additive proposed by JECFA in 1973 and assuming that a 10-kg child consumes 1 litre of water per day, in view of the possibility of zinc complexation. The value was considered provisional to reflect the fact that the JECFA ADI had not been considered since 1973. JECFA further evaluated the toxicological studies available on EDTA in 1993 and was unable to add any further important information regarding the toxicity of EDTA and its calcium and sodium salts to the 1973 evaluation. In the addendum to the second edition of the Guidelines, published in 1998, a guideline value of 0.6 mg/litre was derived for EDTA (free acid), using different assumptions from those used in the derivation of the provisional guideline value in the 1993 Guidelines. In particular, it was noted that the ability of EDTA to complex, and therefore reduce the availability of, zinc was of significance only at elevated doses substantially in excess of those encountered in the environment.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Edetic acid (EDTA) in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/58).

12.57 Endosulfan

Endosulfan (CAS No. 115-29-7) is an insecticide used in countries throughout the world to control pests on fruit, vegetables and tea and on non-food crops such as tobacco and cotton. In addition to its agricultural use, it is used in the control of the tsetse fly, as a wood preservative and for the control of home garden pests. Endosulfan contamination does not appear to be widespread in the aquatic environment, but the chemical has been found in agricultural runoff and rivers in industrialized areas where it is manufactured or formulated, as well as in surface water and groundwater samples collected from hazardous waste sites in the USA. Surface water samples in the USA generally contain less than 1 µg/litre. The main source of exposure of the general population is food, but residues have generally been found to be well below the FAO/WHO maximum residue limits. Another important route of exposure to endosulfan for the general population is the use of tobacco products.

JMPR concluded that endosulfan is not genotoxic, and no carcinogenic effects were noted in long-term studies using mice and rats. The kidney is the target organ for toxicity. Several recent studies have shown that endosulfan, alone or in combination with other pesticides, may bind to estrogen receptors and perturb the endocrine system. A

health-based value of 20 µg/litre can be calculated for endosulfan on the basis of an ADI of 0.006 mg/kg of body weight, based on results from a 2-year dietary study of toxicity in rats, and supported by a 78-week study in mice, a 1-year study in dogs and a developmental toxicity study in rats. However, because endosulfan occurs at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a guideline value.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to endosulfan, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Endosulfan was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- FAO/WHO (1999) *Pesticide residues in food – 1998 evaluations. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/99.18).
- WHO (2003) *Endosulfan in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/92).

12.58 Endrin

Endrin (CAS No. 72-20-8) is a broad-spectrum foliar insecticide that acts against a wide range of agricultural pests. It is also used as a rodenticide. Small amounts of endrin are present in food, but the total intake from food appears to be decreasing.

Guideline value	0.0006 mg/litre (0.6 µg/litre)
Occurrence	Traces of endrin found in the drinking-water supplies of several countries
PTDI	0.0002 mg/kg of body weight, based on a NOAEL of 0.025 mg/kg of body weight per day in a 2-year study in dogs and applying an uncertainty factor of 100
Limit of detection	0.002 µg/litre by GC with ECD
Treatment achievability	0.2 µg/litre should be achievable using GAC

Guideline derivation	
● allocation to water	10% of PTDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	Endrin is listed under the Stockholm Convention on Persistent Organic Pollutants. Hence, monitoring may occur in addition to that required by drinking-water guidelines.

Toxicological review

Toxicological data are insufficient to indicate whether endrin is a carcinogenic hazard to humans. The primary site of action of endrin is the central nervous system.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to endrin, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Endrin was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- FAO/WHO (1995) *Pesticide residues in food – 1994. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment Groups*. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper 127).
- IPCS (1992) *Endrin*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 130).
- WHO (2003) *Endrin in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/93).

12.59 Epichlorohydrin

Epichlorohydrin is used for the manufacture of glycerol, unmodified epoxy resins and water treatment resins. No quantitative data are available on its occurrence in food or drinking-water. Epichlorohydrin is hydrolysed in aqueous media.

12. CHEMICAL FACT SHEETS

Provisional guideline value	0.0004 mg/litre (0.4 µg/litre) The guideline value is considered to be provisional because of the uncertainties surrounding the toxicity of epichlorohydrin and the use of a large uncertainty factor in deriving the guideline value.
Occurrence	No quantitative data available
TDI	0.14 µg/kg of body weight, on the basis of a LOAEL of 2 mg/kg of body weight per day for forestomach hyperplasia observed in a 2-year gavage study in rats, correcting for 5 days per week dosing and using an uncertainty factor of 10 000 to take into consideration inter- and intraspecies variation (100), the use of a LOAEL instead of a NOAEL (10) and carcinogenicity (10)
Limit of detection	0.01 µg/litre by GC with ECD; 0.1 and 0.5 µg/litre by GC/MS; 0.01 mg/litre by GC with FID
Treatment achievability	Conventional treatment processes do not remove epichlorohydrin. Epichlorohydrin concentrations in drinking- water are controlled by limiting either the epichlorohydrin content of polyamine flocculants or the dose used, or both.
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	Although epichlorohydrin is a genotoxic carcinogen, the use of the linearized multistage model for estimating cancer risk was considered inappropriate because tumours are seen only at the site of administration, where epichlorohydrin is highly irritating.

Toxicological review

Epichlorohydrin is rapidly and extensively absorbed following oral, inhalation or dermal exposure. It binds easily to cellular components. Major toxic effects are local irritation and damage to the central nervous system. It induces squamous cell carcinomas in the nasal cavity by inhalation and forestomach tumours by the oral route. It has been shown to be genotoxic *in vitro* and *in vivo*. IARC has placed epichlorohydrin in Group 2A (probably carcinogenic to humans).

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to epichlorohydrin. The 1993 Guidelines proposed a provisional health-based guideline value of 0.0004 mg/litre for epichlorohydrin. The value was provisional because it was derived using an uncertainty factor of 10 000. It was noted that a practical quantification level for epichlorohydrin is of the order of 0.03 mg/litre, but concentrations in drinking-water can be controlled by specifying the epichlorohydrin content of products coming into contact with it.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Epichlorohydrin in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/94).

12.60 Ethylbenzene

The primary sources of ethylbenzene in the environment are the petroleum industry and the use of petroleum products. Because of its physical and chemical properties, more than 96% of ethylbenzene in the environment can be expected to be present in air. Values of up to 26 µg/m³ in air have been reported. Ethylbenzene is found in trace amounts in surface water, groundwater, drinking-water and food.

Guideline value	0.3 mg/litre
Occurrence	Concentrations in drinking-water are generally below 1 µg/litre; levels up to 300 µg/litre have been reported in groundwater contaminated by point emissions.
TDI	97.1 µg/kg of body weight, based on a NOAEL of 136 mg/kg of body weight per day for hepatotoxicity and nephrotoxicity observed in a limited 6-month study in rats, correcting for 5 days per week dosing and using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the limited database and short duration of the study)
Limit of detection	0.002–0.005 µg/litre by GC with photoionization detector; 0.03–0.06 µg/litre by GC/MS
Treatment achievability	0.001 mg/litre should be achievable using air stripping
Guideline derivation	
• allocation to water	10% of TDI
• weight	60-kg adult
• consumption	2 litres/day
Additional comments	The guideline value exceeds the lowest reported odour threshold for ethylbenzene in drinking-water (0.002 mg/litre).

Toxicological review

Ethylbenzene is readily absorbed by oral, inhalation or dermal routes. In humans, storage in fat has been reported. Ethylbenzene is almost completely converted to soluble metabolites, which are excreted rapidly in urine. The acute oral toxicity is low. No definite conclusions can be drawn from limited teratogenicity data. No data on reproduction, long-term toxicity or carcinogenicity are available. Ethylbenzene has shown no evidence of genotoxicity in *in vitro* or in *in vivo* systems.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to ethylbenzene. The 1993 Guidelines proposed a health-based guideline value of 0.3 mg/litre for ethylbenzene, noting that this value exceeds the lowest reported odour threshold for ethylbenzene in drinking-water (0.002 mg/litre).

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Ethylbenzene in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/26).

12.61 Fenitrothion

Fenitrothion (CAS No. 122-14-5) is mainly used in agriculture for controlling insects on rice, cereals, fruits, vegetables, stored grains and cotton and in forest areas. It is also used for the control of flies, mosquitos and cockroaches in public health programmes and/or indoor use. Fenitrothion is stable in water only in the absence of sunlight or microbial contamination. In soil, biodegradation is the primary route of degradation, although photolysis may also play a role. Fenitrothion residues detected in water were low (maximum 1.30 µg/litre) during the spruce budworm spray programme. Following the spraying of forests to control spruce budworm, water samples did not contain detectable amounts of fenitrothion; post-spray samples contained <0.01 µg/litre. Levels of fenitrothion residues in fruits, vegetables and cereal grains decline rapidly after treatment, with a half-life of 1–2 days. Intake of fenitrothion appears to be primarily (95%) from food.

On the basis of testing in an adequate range of studies *in vitro* and *in vivo*, JMPR concluded that fenitrothion is unlikely to be genotoxic. It also concluded that fenitrothion is unlikely to pose a carcinogenic risk to humans. In long-term studies of toxicity, inhibition of cholinesterase activity was the main toxicological finding in all species. A health-based value of 8 µg/litre can be calculated for fenitrothion on the basis of an ADI of 0.005 mg/kg of body weight, based on a NOAEL of 0.5 mg/kg of body weight per day for inhibition of brain and erythrocyte cholinesterase activity in a 2-year study of toxicity in rats and supported by a NOAEL of 0.57 mg/kg of body weight per day for inhibition of brain and erythrocyte cholinesterase activity in a 3-month study of ocular toxicity in rats and a NOAEL of 0.65 mg/kg of body weight per day for reduced food consumption and body weight gain in a study of reproductive toxicity in rats, and allocating 5% of the ADI to drinking-water. However, because

fenitrothion occurs at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a guideline value.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to fenitrothion, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Fenitrothion was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (2001) *Pesticide residues in food – 2000 evaluations. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/01.3).

WHO (2003) *Fenitrothion in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/95).

12.62 Fenoprop (2,4,5-TP; 2,4,5-trichlorophenoxy propionic acid)

The half-lives for degradation of chlorophenoxy herbicides, including fenoprop (CAS No. 93-72-1), in the environment are in the order of several days. Chlorophenoxy herbicides are not often found in food.

Guideline value	0.009 mg/litre
Occurrence	Chlorophenoxy herbicides not frequently found in drinking- water; when detected, concentrations are usually no greater than a few micrograms per litre
TDI	3 µg/kg of body weight, based on a NOAEL of 0.9 mg/kg of body weight for adverse effects on the liver in a study in which beagle dogs were administered fenoprop in the diet for 2 years, with an uncertainty factor of 300 (100 for inter- and intraspecies variation and 3 for limitations in the database)
Limit of detection	0.2 µg/litre by either packed or capillary column GC with ECD
Treatment achievability	No data found; 0.001 mg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

Chlorophenoxy herbicides, as a group, have been classified in Group 2B by IARC. However, the available data from studies in exposed populations and animals do not permit assessment of the carcinogenic potential to humans of any specific chlorophenoxy herbicide. Therefore, drinking-water guidelines for these compounds are based on a threshold approach for other toxic effects. Effects observed in long-term studies with beagle dogs given fenoprop in the diet include mild degeneration and necrosis of hepatocytes and fibroblastic proliferation in one study and severe liver pathology in another study. In rats, increased kidney weight was observed in two long-term dietary studies.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to chlorophenoxy herbicides, including fenoprop, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Fenoprop was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines established a health-based guideline value of 0.009 mg/litre for fenoprop.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/44).

12.63 Fluoride¹

Fluorine is a common element that is widely distributed in the earth's crust and exists in the form of fluorides in a number of minerals, such as fluorspar, cryolite and fluorapatite. Traces of fluorides are present in many waters, with higher concentrations often associated with underground sources. In areas rich in fluoride-containing minerals, well water may contain up to about 10 mg of fluoride per litre, although much higher concentrations can be found. High fluoride concentrations can be found in many parts of the world, particularly in parts of India, China, Central Africa and South America, but high concentrations can be encountered locally in most parts of the

¹ As fluoride is one of the chemicals of greatest health concern in some natural waters, its chemical fact sheet has been expanded.

world. Virtually all foodstuffs contain at least traces of fluorine. All vegetation contains some fluoride, which is absorbed from soil and water. Tea in particular can contain high fluoride concentrations, and levels in dry tea are on average 100 mg/kg.

Fluoride is widely used in dental preparations to combat dental caries, particularly in areas of high sugar intake. These can be in the form of tablets, mouthwashes, toothpaste, varnishes and gels for local application. In some countries, fluoride may also be added to table salt or drinking-water in order to provide protection against dental caries. The amounts added to drinking-water are such that final concentrations are between 0.5 and 1 mg/litre. The fluoride in final water is always present as fluoride ions, whether from natural sources or from artificial fluoridation.

Total daily fluoride exposure can vary markedly from one region to another. This will depend on the concentration of fluoride in drinking-water and the amount drunk, levels in foodstuffs and the use of fluoridated dental preparations. In addition, fluoride exposure in some areas is considerably higher as a consequence of a range of practices, including the consumption of brick tea and the cooking and drying of food with high-fluoride coal.

Guideline value	1.5 mg/litre
Occurrence	In groundwater, concentrations vary with the type of rock the water flows through but do not usually exceed 10 mg/litre; the highest natural level reported is 2800 mg/litre.
Basis of guideline derivation	Epidemiological evidence that concentrations above this value carry an increasing risk of dental fluorosis, and progressively higher concentrations lead to increasing risks of skeletal fluorosis. The value is higher than that recommended for artificial fluoridation of water supplies, which is usually 0.5–1.0 mg/litre.
Limit of detection	0.01 mg/litre by IC; 0.1 mg/litre by ion-selective electrodes or the sulfo phenyl azo dihydroxy naphthalene disulfonic acid (SPADNS) colorimetric method
Treatment achievability	1 mg/litre should be achievable using activated alumina (not a “conventional” treatment process, but relatively simple to install filters)
Additional comments	<ul style="list-style-type: none"> • A management guidance document on fluoride is available (Fawell et al., 2006). • In setting national standards for fluoride or in evaluating the possible health consequences of exposure to fluoride, it is essential to consider the intake of water by the population of interest and the intake of fluoride from other sources (e.g., from food, air and dental preparations). Where the intakes from other sources are likely to approach, or be greater than, 6 mg/day, it would be appropriate to consider setting standards at a lower concentration than the guideline value. • In areas with high natural fluoride levels in drinking-water, the guideline value may be difficult to achieve, in some circumstances, with the treatment technology available.

Toxicological review

After oral uptake, water-soluble fluorides are rapidly and almost completely absorbed from the gastrointestinal tract, although this may be reduced by complex formation with aluminium, phosphorus, magnesium or calcium. There is no difference in absorption between natural or added fluoride in drinking-water. Fluoride in inhaled particles, for example, from high-fluoride coal, is also absorbed, depending on particle size and solubility of fluoride compounds present. Absorbed fluoride is rapidly distributed through the body, where it is incorporated into teeth and bones, with virtually no storage in soft tissues. Fluoride in teeth and bone can be mobilized after external exposure has ceased or been reduced. Fluoride is excreted via urine, faeces and sweat.

Fluoride may be an essential element for humans; however, essentiality has not been demonstrated unequivocally. Meanwhile, there is evidence of fluoride being a beneficial element with regard to the prevention of dental caries.

To produce signs of acute fluoride intoxication, minimum oral doses of about 1 mg of fluoride per kilogram of body weight were required. Many epidemiological studies of possible adverse effects of the long-term ingestion of fluoride via drinking-water have been carried out. These studies clearly establish that high fluoride intakes primarily produce effects on skeletal tissues (bones and teeth). Low concentrations provide protection against dental caries, both in children and in adults. The protective effects of fluoride increase with concentration up to about 2 mg of fluoride per litre of drinking-water; the minimum concentration of fluoride in drinking-water required to produce it is approximately 0.5 mg/litre. However, fluoride can also have an adverse effect on tooth enamel and may give rise to mild dental fluorosis (prevalence: 12–33%) at drinking-water concentrations between 0.9 and 1.2 mg/litre, depending on drinking-water intake and exposure to fluoride from other sources. Mild dental fluorosis may not be detectable except by specialist examination. The risk of dental fluorosis will depend on the total intake of fluoride from all sources and not just the concentration in drinking-water.

Elevated fluoride intakes can have more serious effects on skeletal tissues. Skeletal fluorosis (with adverse changes in bone structure) may be observed when drinking-water contains 3–6 mg of fluoride per litre, particularly with high water consumption. Crippling skeletal fluorosis usually develops only where drinking-water contains over 10 mg of fluoride per litre. IPCS (2002) concluded that there is clear evidence from India and China that skeletal fluorosis and an increased risk of bone fractures occur at a total intake of 14 mg of fluoride per day. This conclusion was supported by a review by the United States National Research Council in 2006 (US NRC, 2006). The relation between exposure and response for adverse effects in bone is frequently difficult to ascertain because of inadequacies in most of the epidemiological studies. IPCS (2002) concluded from estimates based on studies from China and India that for a total intake of 14 mg/day, there is a clear excess risk of skeletal adverse effects;

and there is suggestive evidence of an increased risk of effects on the skeleton at total fluoride intakes above about 6 mg/day.

Several epidemiological studies are available on the possible association between fluoride in drinking-water and cancer. IPCS (2002) evaluated these studies and concluded that overall the evidence of carcinogenicity in laboratory animals is inconclusive and that the available evidence does not support the hypothesis that fluoride causes cancer in humans; however, the data on bone cancer are relatively limited. The results of several epidemiological studies on the possible adverse effects of fluoride in drinking-water on pregnancy outcome indicate that there is no relationship between the rates of Down syndrome or congenital malformation and the consumption of fluoridated drinking-water.

There is no evidence to suggest that the guideline value of 1.5 mg/litre set in 1984 and reaffirmed in 1993 needs to be revised. Concentrations above this value carry an increasing risk of dental fluorosis, and much higher concentrations lead to skeletal fluorosis. The value is higher than that recommended for artificial fluoridation of water supplies, which is usually 0.5–1.0 mg/litre.

In setting national standards or local guidelines for fluoride or in evaluating the possible health consequences of exposure to fluoride, it is essential to consider the average daily intake of water by the population of interest and the intake of fluoride from other sources (e.g., from food and air). Where the intakes are likely to approach, or be greater than, 6 mg/day, it would be appropriate to consider setting a standard or local guideline at a concentration lower than 1.5 mg/litre.

Practical considerations

Fluoride is usually determined by means of an ion-selective electrode, which makes it possible to measure the total amount of free and complex-bound fluoride dissolved in water. The method can detect fluoride concentrations in water well below the guideline value. However, appropriate sample preparation is a critical step in the accurate quantification of fluoride, especially where only the free fluoride ion is measured (Fawell et al., 2006).

A range of treatment technologies are available for both large and small supplies. Different methods for small supplies are favoured in different countries; these are based on bone charcoal, contact precipitation, activated alumina and clay (Fawell et al., 2006). However, in some areas with high natural fluoride levels in drinking-water, the guideline value may be difficult to achieve in some circumstances with the treatment technology available. Large supplies tend to rely on activated alumina or advanced treatment processes such as reverse osmosis.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* referred to fluoride, stating that concentrations in drinking-water in excess of 1.0–1.5 mg of fluorine per litre may give rise to dental fluorosis in some children, and much higher

concentrations may eventually result in skeletal damage in both children and adults. To prevent the development of dental caries in children, a number of communal water supplies are fluoridated to bring the fluorine concentration to 1.0 mg/litre. The 1971 International Standards recommended control limits for fluorides in drinking-water for various ranges of the annual average of maximum daily air temperatures; control limits ranged from 0.6–0.8 mg/litre for temperatures of 26.3–32.6°C to 0.9–1.7 mg/litre for temperatures of 10–12°C. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 1.5 mg/litre was established for fluoride, as mottling of teeth has been reported very occasionally at higher levels. It was also noted that local application of the guideline value must take into account climatic conditions and higher levels of water intake. The 1993 Guidelines concluded that there was no evidence to suggest that the guideline value of 1.5 mg/litre set in 1984 needed to be revised. It was also recognized that in areas with high natural fluoride levels, the guideline value may be difficult to achieve in some circumstances with the treatment technology available. It was emphasized that in setting national standards for fluoride, it is particularly important to consider climatic conditions, volume of water intake and intake of fluoride from other sources.

Assessment date

The risk assessment was conducted in 2003 for the third edition. An expanded summary statement based on the risk assessment was prepared for the second addendum to the third edition.

Principal references

- Fawell J et al. (2006) *Fluoride in drinking-water*. London, IWA Publishing, on behalf of the World Health Organization (WHO Drinking-water Quality Series).
- IPCS (2002) *Fluorides*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 227).
- US NRC (2006) *Fluoride in drinking water: A scientific review of EPA's standards*. Washington, DC, United States National Research Council, National Academies Press.
- WHO (2003) *Fluoride in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/96).

12.64 Formaldehyde

Formaldehyde occurs in industrial effluents and is emitted into air from plastic materials and resin glues. Formaldehyde in drinking-water results primarily from the oxidation of natural organic matter during ozonation and chlorination. Concentrations of up to 30 µg/litre have been found in ozonated drinking-water. Formaldehyde can also be found in drinking-water as a result of release from polyacetal plastic fittings.

Formaldehyde's physicochemical properties suggest that it is unlikely to volatilize from water, so exposure by inhalation during showering is expected to be low.

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. Ingestion of formaldehyde in drinking-water for 2 years caused stomach irritation in rats. Papillomas of the stomach associated with severe tissue irritation were observed in one study. IARC has classified formaldehyde in Group 1 (carcinogenic to humans). The weight of evidence indicates that formaldehyde is not carcinogenic by the oral route.

Owing to formaldehyde's high reactivity, effects in the tissue of first contact following ingestion are more likely to be related to the concentration of the formaldehyde consumed than to its total intake. A tolerable concentration of 2.6 mg/litre for ingested formaldehyde has been established based on a NOEL of 260 mg/litre for histopathological effects in the oral and gastric mucosa of rats administered formaldehyde in their drinking-water for 2 years, using an uncertainty factor of 100 (10 for interspecies variation and 10 for intraspecies variation). In view of the significant difference between the expected concentrations of formaldehyde in drinking-water and the tolerable concentration, it is not considered necessary to set a formal guideline value for formaldehyde.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to formaldehyde. The second edition of the Guidelines established a health-based guideline value of 0.9 mg/litre for formaldehyde in drinking-water. This value was brought forward to the third edition.

Assessment date

The risk assessment was conducted in 2004.

Principal references

IPCS (2002) *Formaldehyde*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 40).

WHO (2005) *Formaldehyde in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/48).

12.65 Glyphosate and AMPA

Glyphosate (CAS No. 1071-83-6) is a broad-spectrum herbicide used in both agriculture and forestry and for aquatic weed control. Microbial biodegradation of glyphosate occurs in soil, aquatic sediment and water, the major metabolite being aminomethylphosphonic acid (AMPA) (CAS No. 1066-51-9). Glyphosate is chemically stable in water and is not subject to photochemical degradation. The low mobility of glyphosate in soil indicates minimal potential for the contamination of groundwater. Glyphosate can, however, enter surface and subsurface waters after direct use near aquatic environments or by runoff or leaching from terrestrial applications.

Glyphosate and AMPA have similar toxicological profiles, and both are considered to exhibit low toxicity. A health-based value of 0.9 mg/litre can be derived based on the group ADI for AMPA alone or in combination with glyphosate of 0.3 mg/kg of body weight, based upon a NOAEL of 32 mg/kg of body weight per day, the highest dose tested, identified in a 26-month study of toxicity in rats fed technical-grade glyphosate and using an uncertainty factor of 100.

Because of their low toxicity, the health-based value derived for AMPA alone or in combination with glyphosate is orders of magnitude higher than concentrations of glyphosate or AMPA normally found in drinking-water. Under usual conditions, therefore, the presence of glyphosate and AMPA in drinking-water does not represent a hazard to human health. For this reason, the establishment of a guideline value for glyphosate and AMPA is not deemed necessary.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to glyphosate, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Glyphosate was not evaluated in the first two editions of the *Guidelines for Drinking-water Quality*, published in 1984 and 1993. In the addendum to these Guidelines, published in 1998, a health-based value of 5 mg/litre was derived for glyphosate using the ADI derived in the EHC monograph for glyphosate published in 1994. However, the health-based value is orders of magnitude higher than the concentrations normally found in drinking-water. Under usual conditions, therefore, the presence of glyphosate in drinking-water does not represent a hazard to human health, and it was not deemed necessary to establish a guideline value for glyphosate. It was noted that most AMPA, the major metabolite of glyphosate, found in water comes from sources other than glyphosate degradation.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- FAO/WHO (1998) *Pesticide residues in food – 1997 evaluations. Part II – Toxicological and environmental*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/98.6).
- IPCS (1994) *Glyphosate*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 159).
- WHO (2003) *Glyphosate and AMPA in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/97).

12.66 Halogenated acetonitriles (dichloroacetonitrile, dibromoacetonitrile, bromochloroacetonitrile, trichloroacetonitrile)

Halogenated acetonitriles are produced during water chlorination or chloramination from naturally occurring substances, including algae, fulvic acid and proteinaceous material. In general, increasing temperature and/or decreasing pH have been associated with increasing concentrations of halogenated acetonitriles. Ambient bromide levels appear to influence, to some degree, the speciation of halogenated acetonitrile compounds. Dichloroacetonitrile is by far the most predominant halogenated acetonitrile species detected in drinking-water.

Provisional guideline value for dichloroacetonitrile	0.02 mg/litre The guideline value for dichloroacetonitrile is provisional due to limitations of the toxicological database.
Guideline value for dibromoacetonitrile	0.07 mg/litre
Occurrence	Halogenated acetonitriles have been found in surface water and groundwater distribution systems at concentrations generally below 10 µg/litre and usually below 1 µg/litre.
TDIs	
Dichloroacetonitrile	2.7 µg/kg of body weight based on a LOAEL of 8 mg/kg of body weight per day for increased relative liver weight in male and female rats in a 90-day study, using an uncertainty factor of 3000 (taking into consideration intra- and interspecies variation, the short duration of the study, the use of a minimal LOAEL and database deficiencies)
Dibromoacetonitrile	11 µg/kg of body weight, based on a NOAEL of 11.3 mg/kg of body weight per day for decreased body weight in male F344 rats in a 90-day drinking-water study and an uncertainty factor of 1000 (accounting for inter- and intraspecies variation, subchronic to chronic extrapolation and database insufficiencies)
Limit of detection	0.03 µg/litre by GC with an ECD

Treatment achievability	Concentrations of individual halogenated acetonitriles can exceed 0.01 mg/litre, although levels of 0.002 mg/litre or less are more usual. Trichloroacetonitrile concentrations are likely to be much less than 0.001 mg/litre. Reduction of organic precursors will reduce their formation.
Guideline derivation	
• allocation to water	20% of TDI
• weight	60-kg adult
• consumption	2 litres/day

Toxicological review

IARC has concluded that dichloro-, dibromo-, bromochloro- and trichloroacetonitrile are not classifiable as to their carcinogenicity in humans. Dichloroacetonitrile and bromochloroacetonitrile have been shown to be mutagenic in bacterial assays, whereas results for dibromoacetonitrile and trichloroacetonitrile were negative. All four of these halogenated acetonitriles induced sister chromatid exchange and DNA strand breaks and adducts in mammalian cells *in vitro* but were negative in the mouse micronucleus test.

The majority of reproductive and developmental toxicity studies of the halogenated acetonitriles were conducted using tricapyrylin as a vehicle for gavage administration of the compound under study. As tricapyrylin was subsequently demonstrated to be a developmental toxicant that potentiated the effects of trichloroacetonitrile and, presumably, other halogenated acetonitriles, results reported for developmental studies using tricapyrylin as the gavage vehicle are likely to overestimate the developmental toxicity of these halogenated acetonitriles.

Dichloroacetonitrile

Dichloroacetonitrile induced decreases in body weight and increases in relative liver weight in short-term studies. Although developmental toxicity has been demonstrated, the studies used tricapyrylin as the vehicle for gavage administration.

Dibromoacetonitrile

Dibromoacetonitrile is currently under test for chronic toxicity in mice and rats. None of the available reproductive or developmental studies were adequate to use in the quantitative dose–response assessment. The data gap may be particularly relevant since cyanide, a metabolite of dibromoacetonitrile, induces male reproductive system toxicity, and due to uncertainty regarding the significance of the testes effects observed in the 14-day National Toxicology Program (NTP) rat study.

Bromochloroacetonitrile

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

Trichloroacetonitrile

Available data are also insufficient to serve as a basis for derivation of a guideline value for trichloroacetonitrile. The previous provisional guideline value of 1 µg/litre was based on a developmental toxicity study in which trichloroacetonitrile was administered by gavage in tricaprylin vehicle, and a recent re-evaluation judged this study to be unreliable in light of the finding in a more recent study that tricaprylin potentiates the developmental and teratogenic effects of halogenated acetonitriles and alters the spectrum of malformations in the fetuses of treated dams.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to halogenated acetonitriles. The 1993 Guidelines established provisional health-based guideline values of 0.09 mg/litre for dichloroacetonitrile, 0.1 mg/litre for dibromoacetonitrile and 0.001 mg/litre for trichloroacetonitrile. The guideline values were designated as provisional because of the limitations of the databases (i.e., lack of long-term toxicity and carcinogenicity bioassays). Available data were insufficient to serve as a basis for derivation of a guideline value for bromochloroacetonitrile.

Assessment date

The risk assessment was conducted in 2003.

Principal references

IPCS (2000) *Disinfectants and disinfectant by-products*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 216).

WHO (2003) *Halogenated acetonitriles in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/98).

12.67 Hardness

Hardness in water is caused by dissolved calcium and, to a lesser extent, magnesium. It is usually expressed as the equivalent quantity of calcium carbonate.

Depending on pH and alkalinity, hardness above about 200 mg/litre can result in scale deposition, particularly on heating. Soft waters with a hardness of less than about 100 mg/litre have a low buffering capacity and may be more corrosive to water pipes.

A number of ecological and analytical epidemiological studies have shown a statistically significant inverse relationship between hardness of drinking-water and cardiovascular disease. There is some indication that very soft waters may have an adverse effect on mineral balance, but detailed studies were not available for evaluation.

No health-based guideline value is proposed for hardness. However, the degree of hardness in water may affect its acceptability to the consumer in terms of taste and scale deposition (see chapter 10).

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to hardness. The 1971 *International Standards* stated that the maximum permissible level of hardness in drinking-water was 10 mEq/litre (500 mg calcium carbonate/litre), based on the acceptability of water for domestic use. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was concluded that there was no firm evidence that drinking hard water causes any adverse effects on human health and that no recommendation on the restriction of municipal water softening or on the maintenance of a minimum residual calcium or magnesium level was warranted. A guideline value of 500 mg/litre (as calcium carbonate) was established for hardness, based on taste and household use considerations. No health-based guideline value for hardness was proposed in the 1993 *Guidelines*, although hardness above approximately 200 mg/litre may cause scale deposition in the distribution system. Public acceptability of the degree of hardness may vary considerably from one community to another, depending on local conditions, and the taste of water with hardness in excess of 500 mg/litre is tolerated by consumers in some instances.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Hardness in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/6).

12.68 Heptachlor and heptachlor epoxide

Heptachlor (CAS No. 76-44-8) is a broad-spectrum insecticide, the use of which has been banned or restricted in many countries. At present, the major use of heptachlor is for termite control by subsurface injection into soil. Heptachlor is quite persistent in soil, where it is mainly transformed to its epoxide. Heptachlor epoxide (CAS No. 1024-57-3) is very resistant to further degradation. Heptachlor and heptachlor epoxide bind to soil particles and migrate very slowly. Heptachlor and heptachlor epoxide have been found in drinking-water at levels of nanograms per litre. Diet is considered to represent the major source of exposure to heptachlor, although intake is decreasing.

Prolonged exposure to heptachlor has been associated with damage to the liver and central nervous system toxicity. In 1991, IARC reviewed the data on heptachlor and concluded that the evidence for carcinogenicity was sufficient in animals and inadequate in humans, classifying it in Group 2B. A health-based value of 0.03 µg/litre can be calculated for heptachlor and heptachlor epoxide on the basis of a PTDI of 0.1 µg/kg of body weight, based on a NOAEL for heptachlor of 0.025 mg/kg of body weight per day from two studies in the dog, taking into consideration inadequacies of the database and allocating 1% of the PTDI to drinking-water. However, because heptachlor and heptachlor epoxide occur at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a guideline value. It should also be noted that concentrations below 0.1 µg/litre are generally not achievable using conventional treatment technology.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to heptachlor and heptachlor epoxide, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.1 µg/litre was recommended for heptachlor and heptachlor epoxide, based on the ADI recommended by JMPR. It was noted that this guideline value was less than the value that would have been calculated by applying the multistage model at a projected incremental cancer risk of 1 per 100 000 per lifetime. The 1993 Guidelines established a health-based guideline value of 0.03 µg/litre for heptachlor, based on an ADI established by JMPR in 1991 and taking into consideration the fact that the main source of exposure seems to be food.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- FAO/WHO (1992) *Pesticide residues in food – 1991. Evaluations – 1991. Part II. Toxicology*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/92.52).
- FAO/WHO (1995) *Pesticide residues in food – 1994. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment Groups*. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper 127).
- WHO (2003) *Heptachlor and heptachlor epoxide in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/99).

12.69 Hexachlorobenzene (HCB)

The major agricultural application for HCB (CAS No. 118-74-1) was as a seed dressing for crops to prevent the growth of fungi, but its use is now uncommon. At present, it appears mainly as a by-product of several chemical processes or an impurity in some pesticides. HCB is distributed throughout the environment because it is mobile and resistant to degradation. It bioaccumulates in organisms because of its physico-chemical properties and its slow elimination. HCB is commonly detected at low levels in food, and it is generally present at low concentrations in ambient air. It has been detected only infrequently, and at very low concentrations (below 0.1 µg/litre), in drinking-water supplies.

IARC has evaluated the evidence for the carcinogenicity of HCB in animals and humans and assigned it to Group 2B. HCB has been shown to induce tumours in three animal species and at a variety of sites. A health-based value of 1 µg/litre can be derived for HCB by applying the linearized multistage low-dose extrapolation model to liver tumours observed in female rats in a 2-year dietary study. Using an alternative (TD₀₅) approach, a health-based guidance value of 0.16 µg/kg body weight per day can be calculated, which corresponds to a drinking-water concentration of approximately 0.05 µg/litre, if one assumes a 1% allocation of the guidance value to drinking-water.

Because the health-based values derived from both of these approaches are considerably higher than the concentrations at which HCB is detected in drinking-water (i.e., sub-nanograms per litre), when it is detected, it is not considered necessary to establish a guideline value for HCB in drinking-water. Hexachlorobenzene is listed under the Stockholm Convention on Persistent Organic Pollutants.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to HCB, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.01 µg/litre was recommended for HCB, derived from the linear multistage extrapolation model for a cancer risk of less than 1 in 100 000 for a lifetime of exposure; it was noted that the mathematical model used involved considerable uncertainty. The 1993 *Guidelines* calculated a guideline value of 1 µg/litre for HCB in drinking-water, corresponding to an upper-bound excess lifetime cancer risk of 10⁻⁵.

Assessment date

The risk assessment was conducted in 2003.

Principal references

IPCS (1997) *Hexachlorobenzene*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 195).

WHO (2003) *Hexachlorobenzene in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/100).

12.70 Hexachlorobutadiene (HCBD)

HCBD is used as a solvent in chlorine gas production, a pesticide, an intermediate in the manufacture of rubber compounds and a lubricant. Concentrations of up to 6 µg/litre have been reported in the effluents from chemical manufacturing plants. It is also found in air and food.

Guideline value	0.0006 mg/litre (0.6 µg/litre)
Occurrence	Has been detected in surface water at concentrations of a few micrograms per litre and in drinking-water at concentrations below 0.5 µg/litre
TDI	0.2 µg/kg of body weight, based on a NOAEL of 0.2 mg/kg of body weight per day for renal toxicity in a 2-year feeding study in rats, using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for limited evidence of carcinogenicity and genotoxicity of some metabolites)
Limit of detection	0.01 µg/litre by GC/MS; 0.18 µg/litre by GC with ECD
Treatment achievability	0.001 mg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	The practical quantification level for HCBD is of the order of 2 µg/litre, but concentrations in drinking-water can be controlled by specifying the HCBD content of products coming into contact with it.

Toxicological review

HCBD is easily absorbed and metabolized via conjugation with glutathione. This conjugate can be further metabolized to a nephrotoxic derivative. Kidney tumours were observed in a long-term oral study in rats. HCBD has not been shown to be carcinogenic by other routes of exposure. IARC has placed HCBD in Group 3. Positive and negative results for HCBD have been obtained in bacterial assays for point mutation; however, several metabolites have given positive results.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not

refer to HCBd. The 1993 Guidelines derived a health-based guideline value of 0.0006 mg/litre for HCBd, noting that although a practical quantification level for HCBd is of the order of 0.002 mg/litre, concentrations in drinking-water can be controlled by specifying the HCBd content of products coming into contact with it.

Assessment date

The risk assessment was conducted in in 2003.

Principal references

IPCS (1994) *Hexachlorobutadiene*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 156).

WHO (2003) *Hexachlorobutadiene in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/101).

12.71 Hydrogen sulfide

Hydrogen sulfide is a gas with an offensive “rotten eggs” odour that is detectable at very low concentrations, below 0.8 µg/m³ in air. It is formed when sulfides are hydrolysed in water. However, the level of hydrogen sulfide found in drinking-water will usually be low, because sulfides are readily oxidized in well aerated water.

The acute toxicity to humans of hydrogen sulfide following inhalation of the gas is high; eye irritation can be observed at concentrations of 15–30 mg/m³. Although oral toxicity data are lacking, it is unlikely that a person could consume a harmful dose of hydrogen sulfide from drinking-water. Consequently, no guideline value is proposed. However, hydrogen sulfide should not be detectable in drinking-water by taste or odour (see chapter 10).

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to hydrogen sulfide. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was recommended that hydrogen sulfide should not be detectable by the consumer, based on aesthetic considerations. A guideline value was not needed, since any contamination can be easily detected by the consumer. The 1993 Guidelines did not propose a health-based guideline value, as oral toxicity data are lacking; nevertheless, it is unlikely that a person could consume a harmful dose of hydrogen sulfide from drinking-water. The taste and odour thresholds of hydrogen sulfide in water are estimated to be between 0.05 and 0.1 mg/litre.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Hydrogen sulfide in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/7).

12.72 Inorganic tin

Tin is used principally in the production of coatings used in the food industry. Food, particularly canned food, therefore represents the major route of human exposure to tin. For the general population, drinking-water is not a significant source of tin, and levels in drinking-water greater than 1–2 µg/litre are exceptional. However, there is increasing use of tin in solder, which may be used in domestic plumbing, and tin has been proposed for use as a corrosion inhibitor.

Tin and inorganic tin compounds are poorly absorbed from the gastrointestinal tract, do not accumulate in tissues and are rapidly excreted, primarily in the faeces.

No increased incidence of tumours was observed in long-term carcinogenicity studies conducted in mice and rats fed stannous chloride. Tin has not been shown to be teratogenic or fetotoxic in mice, rats or hamsters. In rats, the NOAEL in a long-term feeding study was 20 mg/kg of body weight per day.

The main adverse effect on humans of excessive levels of tin in canned beverages (above 150 mg/kg) or other canned foods (above 250 mg/kg) has been acute gastric irritation. There is no evidence of adverse effects in humans associated with chronic exposure to tin.

In 1989, JECFA established a PTWI of 14 mg/kg of body weight from a TDI of 2 mg/kg of body weight on the basis that the problem with tin is associated with acute gastrointestinal irritancy, the threshold for which is about 200 mg/kg in food. This was reaffirmed by JECFA in 2000. In view of its low toxicity, the presence of tin in drinking-water does not, therefore, represent a hazard to human health. For this reason, the establishment of a guideline value for inorganic tin is not deemed necessary.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to inorganic tin. The 1971 *International Standards* stated that tin should be controlled in drinking-water, but that insufficient information was available to enable a tentative limit to be established. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was concluded that no action was required for tin. The establishment of a guideline value for inorganic tin was not deemed necessary in the 1993 *Guidelines*, as, because of the low toxicity of inorganic tin, a tentative guideline value could be derived 3 orders of magnitude higher than the normal tin concentration in drinking-water. Therefore, the presence of tin in drinking-water does not represent a hazard to human health.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Inorganic tin in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/115).

12.73 Iodine

Iodine occurs naturally in water in the form of iodide. Traces of iodine are produced by oxidation of iodide during water treatment. Iodine is occasionally used for water disinfection in the field or in emergency situations.

Iodine is an essential element for the synthesis of thyroid hormones. Estimates of the dietary requirement for adult humans range from 80 to 150 µg/day; in many parts of the world, there are dietary deficiencies in iodine. In 1988, JECFA set a PMTDI for iodine of 1 mg/day (17 µg/kg of body weight per day) from all sources, based primarily on data on the effects of iodide. 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.

Available data therefore suggest that derivation of a guideline value for iodine on the basis of information on the 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 concentrations such as might occur from water disinfection is unlikely. For these reasons, a guideline value for iodine has not been established at this time. There is, however, a need for guidance concerning the use of iodine as a disinfectant in emergency situations and for travellers.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to iodine. The 1993 Guidelines did not establish a guideline value for iodine because available data suggest that derivation of a guideline value for iodine on the basis of information on the effects of iodide is inappropriate and there are few relevant data on the effects of iodine; also, because iodine is not recommended for long-term disinfection, lifetime exposure to iodine concentrations such as might occur from water disinfection is unlikely.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Iodine in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/46).

12.74 Iron

Iron is one of the most abundant metals in the Earth's crust. It is found in natural fresh waters at levels ranging from 0.5 to 50 mg/litre. Iron may also be present in drinking-water as a result of the use of iron coagulants or the corrosion of steel and cast iron pipes during water distribution.

Iron is an essential element in human nutrition. Estimates of the minimum daily requirement for iron depend on age, sex, physiological status and iron bioavailability and range from about 10 to 50 mg/day.

As a precaution against storage in the body of excessive iron, in 1983 JECFA established a PMTDI of 0.8 mg/kg of body weight, which applies to iron from all sources except for iron oxides used as colouring agents and iron supplements taken during pregnancy and lactation or for specific clinical requirements. An allocation of 10% of this PMTDI to drinking-water gives a value of about 2 mg/litre, which does not present a hazard to health. The taste and appearance of drinking-water will usually be affected below this level (see chapter 10).

No guideline value for iron in drinking-water is proposed.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* suggested that concentrations of iron greater than 1.0 mg/litre would markedly impair the potability of the water. The 1963 and 1971 International Standards retained this value as a maximum allowable or permissible concentration. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 0.3 mg/litre was established, as a compromise between iron's use in water treatment and aesthetic considerations. No health-based guideline value for iron in drinking-water was proposed in the 1993 Guidelines, but it was mentioned that a value of about 2 mg/litre can be derived from the PMTDI established in 1983 by JECFA as a precaution against storage in the body of excessive iron. Iron stains laundry and plumbing fixtures at levels above 0.3 mg/litre; there is usually no noticeable taste at iron concentrations below 0.3 mg/litre, and concentrations of 1–3 mg/litre can be acceptable for people drinking anaerobic well water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Iron in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/8).

12.75 Isoproturon

Isoproturon (CAS No. 34123-59-6) is a selective, systemic herbicide used in the control of annual grasses and broad-leaved weeds in cereals. It can be photodegraded, hydrolysed and biodegraded and persists for periods ranging from days to weeks. It is mobile in soil. There is evidence that exposure to this compound through food is low.

Guideline value	0.009 mg/litre
Occurrence	Has been detected in surface water and groundwater, usually at concentrations below 0.1 µg/litre; levels above 0.1 µg/litre have occasionally been detected in drinking-water
TDI	3 µg/kg of body weight based on a NOAEL of approximately 3 mg/kg of body weight in a 90-day study in dogs and a 2-year Feeding study in rats, with an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for evidence of non-genotoxic carcinogenicity in rats)
Limit of detection	10–100 ng/litre by reverse-phase HPLC followed by UV or electrochemical detection
Treatment achievability	0.1 µg/litre should be achievable using ozonation
Guideline derivation	
• allocation to water	10% of TDI
• weight	60-kg adult
• consumption	2 litres/day

Toxicological review

Isoproturon is of low acute toxicity and low to moderate toxicity following short- and long-term exposures. It does not possess significant genotoxic activity, but it causes marked enzyme induction and liver enlargement. Isoproturon caused an increase in hepatocellular tumours in male and female rats, but this was apparent only at doses that also caused liver toxicity. Isoproturon appears to be a tumour promoter rather than a complete carcinogen.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to isoproturon, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Isoproturon was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in

1984, but the 1993 Guidelines calculated a health-based guideline value of 0.009 mg/litre for isoproturon in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Isoproturon in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/37).

12.76 Lead

Lead is used principally in the production of lead-acid batteries, solder and alloys. The organolead compounds tetraethyl and tetramethyl lead have also been used extensively as antiknock and lubricating agents in petrol, although their use for these purposes in many countries is being phased out. Owing to the decreasing use of lead-containing additives in petrol and of lead-containing solder in the food processing industry, concentrations in air and food are declining, and intake from drinking-water constitutes a greater proportion of total intake. Lead is rarely present in tap water as a result of its dissolution from natural sources; rather, its presence is primarily from household plumbing systems containing lead in pipes, solder, fittings or the service connections to homes. The amount of lead dissolved from the plumbing system depends on several factors, including pH, temperature, water hardness and standing time of the water, with soft, acidic water being the most plumbosolvent.

Guideline value	0.01 mg/litre
Occurrence	Concentrations in drinking-water are generally below 5 µg/litre, although much higher concentrations (above 100 µg/litre) have been measured where lead fittings are present.
PTWI	25 µg/kg of body weight (equivalent to 3.5 µg/kg of body weight per day) for infants and children on the basis that lead is a cumulative poison and that there should be no accumulation of body burden of lead
Limit of detection	1 µg/litre by AAS
Treatment achievability	Not a raw water contaminant; treatment not applicable
Guideline derivation	
● allocation to water	50% of PTWI
● weight	5-kg infant
● consumption	0.75 litre/day

Additional comments

- As infants are considered to be the most sensitive subgroup of the population, this guideline value will also be protective for other age groups.
 - Lead is exceptional in that most lead in drinking-water arises from plumbing in buildings and the remedy consists principally of removing plumbing and fittings containing lead. This requires much time and money, and it is recognized that not all water will meet the guideline immediately. Meanwhile, all other practical measures to reduce total exposure to lead, including corrosion control, should be implemented.
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Toxicological review

Placental transfer of lead occurs in humans as early as the 12th week of gestation and continues throughout development. Young children absorb 4–5 times as much lead as adults, and the biological half-life may be considerably longer in children than in adults. Lead is a general toxicant that accumulates in the skeleton. Infants, children up to 6 years of age and pregnant women are most susceptible to its adverse health effects. Inhibition of the activity of d-aminolaevulinic dehydratase (porphobilinogen synthase; one of the major enzymes involved in the biosynthesis of haem) in children has been observed at blood lead levels as low as 5 µg/dl, although adverse effects are not associated with its inhibition at this level. Lead also interferes with calcium metabolism, both directly and by interfering with vitamin D metabolism. These effects have been observed in children at blood lead levels ranging from 12 to 120 µg/dl, with no evidence of a threshold. Lead is toxic to both the central and peripheral nervous systems, inducing subencephalopathic neurological and behavioural effects. There is electrophysiological evidence of effects on the nervous system in children with blood lead levels well below 30 µg/dl. The balance of evidence from cross-sectional epidemiological studies indicates that there are statistically significant associations between blood lead levels of 30 µg/dl and more and intelligence quotient deficits of about four points in children. Results from prospective (longitudinal) epidemiological studies suggest that prenatal exposure to lead may have early effects on mental development that do not persist to the age of 4 years. Research on primates has supported the results of the epidemiological studies, in that significant behavioural and cognitive effects have been observed following postnatal exposure resulting in blood lead levels ranging from 11 to 33 µg/dl. Renal tumours have been induced in experimental animals exposed to high concentrations of lead compounds in the diet, and IARC has classified lead and inorganic lead compounds in Group 2B (possible human carcinogen). However, there is evidence from studies in humans that adverse neurotoxic effects other than cancer may occur at very low concentrations of lead and that a guideline value derived on this basis would also be protective for carcinogenic effects.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* recommended a maximum allowable concentration of 0.1 mg/litre for lead, based on health concerns.

This value was lowered to 0.05 mg/litre in the 1963 International Standards. The tentative upper concentration limit was increased to 0.1 mg/litre in the 1971 International Standards, because this level was accepted in many countries and the water had been consumed for many years without apparent ill effects, and it was difficult to reach a lower level in countries where lead pipes were used. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.05 mg/litre was recommended. The 1993 Guidelines proposed a health-based guideline value of 0.01 mg/litre, using the PTWI established by JECFA for infants and children, on the basis that lead is a cumulative poison and that there should be no accumulation of body burden of lead. As infants are considered to be the most sensitive subgroup of the population, this guideline value would also be protective for other age groups. The Guidelines also recognized that lead is exceptional, in that most lead in drinking-water arises from plumbing, and the remedy consists principally of removing plumbing and fittings containing lead. As this requires much time and money, it is recognized that not all water will meet the guideline immediately. Meanwhile, all other practical measures to reduce total exposure to lead, including corrosion control, should be implemented. JECFA has reassessed lead and confirmed the previously derived PTWI.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Lead in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/9).

12.77 Lindane

Lindane (γ -hexachlorocyclohexane, γ -HCH) (CAS No. 58-89-9) is used as an insecticide on fruit and vegetable crops, for seed treatment and in forestry. It is also used as a therapeutic pesticide in humans and animals. Several countries have restricted the use of lindane. Lindane can be degraded in soil and rarely leaches to groundwater. In surface waters, it can be removed by evaporation. Exposure of humans occurs mainly via food, but this is decreasing. There may also be exposure from its use in public health and as a wood preservative.

12. CHEMICAL FACT SHEETS

Guideline value	0.002 mg/litre
Occurrence	Has been detected in both surface water and groundwater, usually at concentrations below 0.1 µg/litre, although concentrations as high as 12 µg/litre have been measured in wastewater-contaminated rivers
ADI	0.005 mg/kg of body weight on the basis of a NOAEL of 0.47 mg/kg of body weight per day in a 2-year toxicity/carcinogenicity study in rats in which an increased incidence of periacinar hepatocellular hypertrophy, increased liver and spleen weights and increased mortality occurred at higher doses, using an uncertainty factor of 100
Limit of detection	0.01 µg/litre using GC
Treatment achievability	0.1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	1% of ADI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

Lindane was toxic to the kidney and liver after administration orally, dermally or by inhalation in short-term and long-term studies of toxicity and reproductive toxicity in rats. The renal toxicity of lindane was specific to male rats and was considered not to be relevant to human risk assessment, since it is a consequence of accumulation of α_{2u} -globulin, a protein that is not found in humans. Hepatocellular hypertrophy was observed in a number of studies in mice, rats and rabbits and was reversed only partially after recovery periods of up to 6 weeks. Lindane did not induce a carcinogenic response in rats or dogs, but it caused an increased incidence of adenomas and carcinomas of the liver in agouti and pseudoagouti mice, but not in black or any other strains of mice, in a study of the role of genetic background in the latency and incidence of tumorigenesis. JMPR has concluded that there was no evidence of genotoxicity. In the absence of genotoxicity and on the basis of the weight of the evidence from the studies of carcinogenicity, JMPR has concluded that lindane is not likely to pose a carcinogenic risk to humans. Further, in an epidemiological study designed to assess the potential association between breast cancer and exposure to chlorinated pesticides, no correlation with lindane was found.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to lindane, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 3 µg/litre was recommended for lindane, based on the ADI recommended by JMPR. The 1993 *Guidelines* established a health-based guideline value of 2 µg/litre for lindane in drinking-water, on the basis of a study used to establish an ADI by JMPR

in 1989 but using a compound intake estimate considered to be more appropriate in light of additional data and recognizing that there may be substantial exposure to lindane from its use in public health and as a wood preservative.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (2002) *Pesticide residues in food – 2002*. Rome, Food and Agriculture Organization of the United Nations, Joint FAO/WHO Meeting on Pesticide Residues (FAO Plant Production and Protection Paper 172).

WHO (2003) *Lindane in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/102).

12.78 Malathion

Malathion (CAS No. 121-75-5) is commonly used to control mosquitos and a variety of insects that attack fruits, vegetables, landscaping plants and shrubs. It can also be found in other pesticide products used indoors, on pets to control ticks and insects and to control human head and body lice. Under least favourable conditions (i.e., low pH and little organic content), malathion may persist in water with a half-life of months or even years. However, under most conditions, the half-life appears to be roughly 7–14 days. Malathion has been detected in surface water and drinking-water at concentrations below 2 µg/litre.

Malathion inhibits cholinesterase activity in mice, rats and human volunteers. It increased the incidence of liver adenomas in mice when administered in the diet. Most of the evidence indicates that malathion is not genotoxic, although some studies indicate that it can produce chromosomal aberrations and sister chromatid exchange *in vitro*. JMPR has concluded that malathion is not genotoxic.

A health-based value of 0.9 mg/litre can be calculated for malathion based on an allocation of 10% of the JMPR ADI – based on a NOAEL of 29 mg/kg of body weight per day in a 2-year study of toxicity and carcinogenicity in rats, using an uncertainty factor of 100 and supported by a NOAEL of 25 mg/kg of body weight per day in a developmental toxicity study in rabbits – to drinking-water. However, intake of malathion from all sources is generally low and well below the ADI. As the chemical occurs in drinking-water at concentrations much lower than the health-based value, the presence of malathion in drinking-water under usual conditions is unlikely to represent a hazard to human health. For this reason, it is considered unnecessary to derive a guideline value for malathion in drinking-water.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to malathion, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Malathion was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (1998) *Pesticide residues in food – 1997 evaluations. Part II – Toxicological and environmental*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/98.6).

WHO (2003) *Malathion in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/103).

12.79 Manganese

Manganese is one of the most abundant metals in the Earth's crust, usually occurring with iron. It is used principally in the manufacture of iron and steel alloys, as an oxidant for cleaning, bleaching and disinfection as potassium permanganate and as an ingredient in various products. More recently, it has been used in an organic compound, MMT, as an octane enhancer in petrol in North America. Manganese greensands are used in some locations for potable water treatment. Manganese is an essential element for humans and other animals and occurs naturally in many food sources. The most important oxidative states for the environment and biology are Mn^{2+} , Mn^{4+} and Mn^{7+} . Manganese is naturally occurring in many surface water and groundwater sources, particularly in anaerobic or low oxidation conditions, and this is the most important source for drinking-water. The greatest exposure to manganese is usually from food.

Guideline value	0.4 mg/litre
Occurrence	Levels in fresh water typically range from 1 to 200 µg/litre, although levels as high as 10 mg/litre in acidic groundwater have been reported; higher levels in aerobic waters usually associated with industrial pollution
TDI	0.06 mg/kg of body weight, based on the upper range value of manganese intake of 11 mg/day, identified using dietary surveys, at which there are no observed adverse effects (i.e., considered a NOAEL), using an uncertainty factor of 3 to take into consideration the possible increased bioavailability of manganese from water
Limit of detection	0.01 µg/litre by AAS; 0.05 µg/litre by ICP/MS; 0.5 µg/litre by ICP/optical emission spectroscopy; 1 µg/litre by EAAS; 10 µg/litre by FAAS
Treatment achievability	0.05 mg/litre should be achievable using oxidation and filtration
Guideline derivation	
● allocation to water	20% of TDI (because manganese is essential trace element)
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	The presence of manganese in drinking-water will be objectionable to consumers if it is deposited in water mains and causes water discoloration. Concentrations below 0.05–0.1 mg/litre are usually acceptable to consumers but may sometimes still give rise to the deposition of black deposits in water mains over an extended period; this may vary with local circumstances.

Toxicological review

Manganese is an essential element for humans and other animals. Adverse effects can result from both deficiency and overexposure. Manganese is known to cause neurological effects following inhalation exposure, particularly in occupational settings, and there have been epidemiological studies that report adverse neurological effects following extended exposure to very high levels in drinking-water. However, there are a number of significant potential confounding factors in these studies, and a number of other studies have failed to observe adverse effects following exposure through drinking-water. Animal data, especially rodent data, are not desirable for human risk assessment because the physiological requirements for manganese vary among different species. Further, rodents are of limited value in assessing the neurobehavioural effects, because the neurological effects (e.g., tremor, gait disorders) seen in primates are often preceded or accompanied by psychological symptoms (e.g., irritability, emotional lability), which are not apparent in rodents. The only primate study is of limited use in a quantitative risk assessment because only one dose group was studied in a small number of animals and the manganese content in the basal diet was not provided.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* suggested that concentrations of manganese greater than 0.5 mg/litre would markedly impair the potability of

the water. The 1963 and 1971 International Standards retained this value as a maximum allowable or permissible concentration. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 0.1 mg/litre was established for manganese, based on its staining properties. The 1993 Guidelines concluded that although no single study is suitable for use in calculating a guideline value, the weight of evidence from actual daily intake and toxicity studies in laboratory animals given manganese in drinking-water supports the view that a provisional health-based guideline value of 0.5 mg/litre should be adequate to protect public health. It was also noted that concentrations below 0.1 mg/litre are usually acceptable to consumers, although this may vary with local circumstances.

Assessment date

The risk assessment was conducted in 2003.

Principal references

IPCS (1999) *Manganese and its compounds*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 12).

WHO (2003) *Manganese in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/104).

12.80 MCPA [4-(2-methyl-4-chlorophenoxy)acetic acid]

MCPA (CAS No. 94-74-6) is a chlorophenoxy post-emergence herbicide that is very soluble, is highly mobile and can leach from the soil. It is metabolized by bacteria and can be photochemically degraded. MCPA has only limited persistence in water.

Guideline value	0.002 mg/litre
Occurrence	Not frequently detected in drinking-water; has been measured in surface water and groundwater at concentrations below 0.54 and 5.5 µg/litre, respectively
TDI	0.5 µg/kg of body weight, based on a NOAEL of 0.15 mg/kg of body weight for renal and liver toxicity observed at higher dose levels in a 1-year feeding study in dogs, with an uncertainty factor of 300 (100 for inter- and intraspecies variation and 3 for inadequacies in the database)
Limit of detection	0.01 µg/litre by GC/MS and by GC with ECD
Treatment achievability	0.1 µg/litre should be achievable using GAC or ozonation
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

There are only limited and inconclusive data on the genotoxicity of MCPA. IARC evaluated MCPA in 1983 and concluded that the available data on humans and experimental animals were inadequate for an evaluation of carcinogenicity. Further evaluations by IARC on chlorophenoxy herbicides in 1986 and 1987 concluded that evidence for their carcinogenicity was limited in humans and inadequate in animals (Group 2B). Recent carcinogenicity studies on rats and mice did not indicate that MCPA was carcinogenic. No adequate epidemiological data on exposure to MCPA alone are available.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to MCPA, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. MCPA was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 *Guidelines* established a health-based guideline value of 0.002 mg/litre for MCPA in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *MCPA in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/38).

12.81 Mecoprop (MCPP; [2(2-methyl-chlorophenoxy) propionic acid])

The half-lives for degradation of chlorophenoxy herbicides, including mecoprop (CAS No. 93-65-2; 7085-19-0 racemic mixture), in the environment are in the order of several days. Chlorophenoxy herbicides are not often found in food.

12. CHEMICAL FACT SHEETS

Guideline value	0.01 mg/litre
Occurrence	Chlorophenoxy herbicides not frequently found in drinking- water; when detected, concentrations are usually no greater than a few micrograms per litre
TDI	3.33 µg/kg of body weight, based on a NOAEL of 1 mg/kg of body weight for effects on kidney weight in 1- and 2-year studies in rats, with an uncertainty factor of 300 (100 for inter- and intraspecies variation and 3 for limitations in the database)
Limit of detection	0.01 µg/litre by GC/MS; 0.01–0.02 µg/litre by GC with ECD
Treatment achievability	0.1 µg/litre should be achievable using GAC or ozonation
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

Chlorophenoxy herbicides, as a group, have been classified in Group 2B by IARC. However, the available data from studies in exposed populations and animals do not permit assessment of the carcinogenic potential to humans of any specific chlorophenoxy herbicide. Therefore, drinking-water guidelines for these compounds are based on a threshold approach for other toxic effects. Effects of dietary administration of mecoprop in short- and long-term studies include decreased relative kidney weight (rats and beagle dogs), increased relative liver weight (rats), effects on blood parameters (rats and beagle dogs) and depressed body weight gain (beagle dogs).

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to chlorophenoxy herbicides, including mecoprop, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Mecoprop was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines established a health-based guideline value of 0.01 mg/litre for mecoprop.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/44).

12.82 Mercury

Mercury is used in the electrolytic production of chlorine, in electrical appliances, in dental amalgams and as a raw material for various mercury compounds. Methylation of inorganic mercury has been shown to occur in fresh water and in seawater, although almost all mercury in uncontaminated drinking-water is thought to be in the form of Hg^{2+} . Thus, it is unlikely that there is any direct risk of the intake of organic mercury compounds, especially of alkylmercurials, as a result of the ingestion of drinking-water. However, there is a possibility that methylmercury will be converted into inorganic mercury. Food is the main source of mercury in non-occupationally exposed populations; the mean dietary intake of mercury in various countries ranges from 2 to 20 $\mu\text{g}/\text{day}$ per person.

Guideline value	0.006 mg/litre for inorganic mercury
Occurrence	Mercury is present in the inorganic form in surface water and groundwater at concentrations usually below 0.5 $\mu\text{g}/\text{litre}$, although local mineral deposits may produce higher levels in groundwater.
TDI	2 $\mu\text{g}/\text{kg}$ of body weight for inorganic mercury based on a NOAEL of 0.23 mg/kg of body weight per day for kidney effects in a 26-week study in rats and applying an uncertainty factor of 100 (for inter- and intraspecies variation) after adjusting for 5 days/week dosing
Limit of detection	0.05 $\mu\text{g}/\text{litre}$ by cold vapour AAS; 0.6 $\mu\text{g}/\text{litre}$ by ICP; 5 $\mu\text{g}/\text{litre}$ by FAAS
Treatment achievability	It should be possible to achieve a concentration below 1 $\mu\text{g}/\text{litre}$ by treatment of raw waters that are not grossly contaminated with mercury using methods that include coagulation/sedimentation/ filtration, PAC and ion exchange.
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	<ul style="list-style-type: none"> ● A similar TDI may be obtained by applying an uncertainty factor of 1000 (an additional uncertainty factor of 10 for adjustment from a LOAEL to a NOAEL) to the LOAEL for renal effects of 1.9 mg/kg of body weight per day in a 2-year NTP study in rats. ● The new guideline value applies to inorganic mercury, which is the form found in drinking-water, whereas the previous guideline value applied to total (inorganic and organic) mercury.

Toxicological review

The toxic effects of inorganic mercury compounds are seen mainly in the kidney in both humans and laboratory animals following short- and long-term exposure. In rats, effects include increased absolute and relative kidney weights, tubular necrosis, proteinuria and hypoalbuminaemia. In humans, acute oral poisoning results primarily in haemorrhagic gastritis and colitis; the ultimate damage is to the kidney. The overall weight of evidence is that mercury(II) chloride has the potential to increase

the incidence of some benign tumours at sites where tissue damage is apparent and that it possesses weak genotoxic activity but does not cause point mutations.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not mention mercury. Mercury was first mentioned in the 1971 *International Standards*, which gave the tentative upper concentration limit for mercury as 0.001 mg/litre (total mercury), based on health concerns. It was noted that this figure was related to levels found in natural water. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, the guideline value of 0.001 mg/litre was retained for total mercury. The 1993 *Guidelines* also retained the guideline value of 0.001 mg/litre for total mercury, based on the PTWI for methylmercury established by JECFA in 1972 and reaffirmed by JECFA in 1988. This value was brought forward to the third edition.

Assessment date

The risk assessment was conducted in 2004.

Principal references

- IPCS (2003) *Elemental mercury and inorganic mercury compounds: human health aspects*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 50).
- WHO (2005) *Mercury in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/10).

12.83 Methoxychlor

Methoxychlor (CAS No. 72-43-5) is an insecticide used on vegetables, fruit, trees, fodder and farm animals. It is poorly soluble in water and highly immobile in most agricultural soils. Under normal conditions of use, methoxychlor does not seem to be of environmental concern. Daily intake from food and air is expected to be below 1 µg per person. Environmental metabolites are formed preferentially under anaerobic rather than aerobic conditions and include mainly the dechlorinated and demethylated products. There is some potential for the accumulation of the parent compound and its metabolites in surface water sediments.

Guideline value	0.02 mg/litre
Occurrence	Detected occasionally in drinking-water, at concentrations as high as 300 µg/litre in rural areas
TDI	5 µg/kg of body weight, based on a systemic NOAEL of 5 mg/kg of body weight in a teratology study in rabbits, with an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 reflecting concern for threshold carcinogenicity and the limited database)

12. CHEMICAL FACT SHEETS

Limit of detection	0.001–0.01 µg/litre by GC
Treatment achievability	0.1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

The genotoxic potential of methoxychlor appears to be negligible. In 1979, IARC assigned methoxychlor to Group 3. Subsequent data suggest a carcinogenic potential of methoxychlor for liver and testes in mice. This may be due to the hormonal activity of proestrogenic mammalian metabolites of methoxychlor and may therefore have

a threshold. The study, however, was inadequate because only one dose was used and because this dose may have been above the maximum tolerated dose. The database for studies on long-term, short-term and reproductive toxicity is inadequate. A teratology study in rabbits reported a systemic NOAEL of 5 mg/kg of body weight per day, which is lower than the LOAELs and NOAELs from other studies. This NOAEL was therefore selected for use in the derivation of a TDI.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to methoxychlor, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.03 mg/litre was recommended for methoxychlor, based on the ADI recommended by JMPR in 1965 and reaffirmed in 1977. The 1993 Guidelines established a health-based guideline value of 0.02 mg/litre for methoxychlor in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Methoxychlor in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/105).

12.84 Methyl parathion

Methyl parathion (CAS No. 298-00-0) is a non-systemic insecticide and acaricide that is produced throughout the world and has been registered for use on many crops, in particular cotton. It partitions mainly to air and soil in the environment. There is virtually no movement through soil, and neither the parent compound nor its breakdown products will reach groundwater. By far the most important route for the environmental degradation of methyl parathion is microbial degradation. Half-lives of methyl parathion in water are in the order of weeks to months. Concentrations of methyl parathion in natural waters of agricultural areas in the USA ranged up to 0.46 µg/litre, with highest levels in summer. The general population can come into contact with methyl parathion via air, water or food.

A NOAEL of 0.3 mg/kg of body weight per day was derived from the combined results of several studies conducted in humans, based on the depression of erythrocyte and plasma cholinesterase activities. Methyl parathion decreased cholinesterase activities in long-term studies in mice and rats, but did not induce carcinogenic

effects. Methyl parathion was mutagenic in bacteria, but there was no evidence of genotoxicity in a limited range of studies in mammalian systems.

A health-based value of 9 µg/litre can be calculated for methyl parathion on the basis of an ADI of 0.003 mg/kg of body weight, based on a NOAEL of 0.25 mg/kg of body weight per day in a 2-year study in rats for retinal degeneration, sciatic nerve demyelination, reduced body weight, anaemia and decreased brain acetylcholinesterase activity, using an uncertainty factor of 100. Since the toxicological end-points seen in animals were other than acetylcholinesterase inhibition, it was considered more appropriate to use these data rather than the NOAEL derived for cholinesterase inhibition in humans.

Intake of methyl parathion from all sources is generally low and well below the ADI. As the health-based value is much higher than methyl parathion concentrations likely to be found in drinking-water, the presence of methyl parathion in drinking-water under usual conditions is unlikely to represent a hazard to human health. For this reason, the establishment of a guideline value for methyl parathion is not deemed necessary.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to methyl parathion, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Methyl parathion was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- FAO/WHO (1996) *Pesticide residues in food – 1995 evaluations. Part II – Toxicological and environmental*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/96.48).
- IPCS (1992) *Methyl parathion*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 145).
- WHO (2003) *Methyl parathion in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/106).

12.84(a) Methyl tertiary-butyl ether (MTBE)

The major use of MTBE is as a gasoline additive. Surface water can be contaminated by gasoline spills; however, due to the high volatility of MTBE, most is lost to evapo-

ration. Spills and leaking storage tanks can cause more serious problems in groundwater, where MTBE is more persistent. MTBE has been detected in groundwater and drinking-water at concentrations in the ng/litre to µg/litre range.

No human cancer studies have been published for either the general population or occupationally exposed cohorts. There have been a number of human studies of neurological and clinical effects of exposure to MTBE by inhalation, with mixed results. In general, no objective changes could be seen at levels of MTBE normally found, even in such microenvironments as gasoline filling stations.

The weight of evidence suggests that MTBE is not genotoxic. A large number of studies using *in vitro* and *in vivo* mammalian and non-mammalian systems have been conducted to assess the mutagenicity of MTBE, almost all of which have produced negative results. These results suggest that the mechanism of action of MTBE is more likely to be non-genotoxic than genotoxic, although no one mechanism appears to explain all of the observed effects.

It has been concluded that MTBE should be considered a rodent carcinogen but that it is not genotoxic, and the carcinogenic response is evident only at high levels of exposure that also induce other adverse effects. The available data are therefore considered inconclusive and prohibit their use for human carcinogenic risk assessment. A health-based guideline value has not been derived for MTBE, due to the fact that any guideline value that would be derived would be significantly higher than the concentration at which it would be detected by odour (15 µg/litre is the lowest level eliciting a response in a study using taste- and odour-sensitive participants).

History of guideline development

MTBE was not evaluated in WHO *International Standards for Drinking-water* or in the first, second or third editions of the *Guidelines for Drinking-water Quality*.

Assessment date

The risk assessment was conducted in 2004.

Principal references

IPCS (1998) *Methyl tertiary-butyl ether*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 206).
WHO (2005) *Methyl tertiary-butyl ether (MTBE) in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/122).

12.85 Metolachlor

Metolachlor (CAS No. 51218-45-2) is a selective pre-emergence herbicide used on a number of crops. It can be lost from the soil through biodegradation, photodegrada-

tion and volatilization. It is fairly mobile and under certain conditions can contaminate groundwater, but it is mostly found in surface water.

Guideline value	0.01 mg/litre
Occurrence	Detected in surface water and groundwater at concentrations that can exceed 10 µg/litre
TDI	3.5 µg/kg of body weight, based on a NOAEL of 3.5 mg/kg of body weight for an apparent decrease in kidney weight at the two highest dose levels in a 1-year dog study, with an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 reflecting some concern regarding carcinogenicity)
Limit of detection	0.75–0.01 µg/litre by GC with nitrogen–phosphorus detection
Treatment achievability	0.1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

In a 1-year study in beagle dogs, administration of metolachlor resulted in decreased kidney weight at the two highest dose levels. In 2-year studies with rodents fed metolachlor in the diet, the only toxicological effects observed in albino mice were decreased body weight gain and decreased survival in females at the highest dose level, whereas rats showed decreased body weight gain and food consumption at the highest dose level. There is no evidence from available studies that metolachlor is carcinogenic in mice. In rats, an increase in liver tumours in females as well as a few nasal tumours in males have been observed. Metolachlor is not genotoxic.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to metolachlor, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Metolachlor was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 *Guidelines* established a health-based guideline value of 0.01 mg/litre for metolachlor in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Metolachlor in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/39).

12.86 Microcystin-LR

Among the more than 80 microcystins identified to date, only a few occur frequently and in high concentrations. Microcystin-LR is among the most frequent and most toxic microcystin congeners. Frequently occurring cyanobacterial genera that contain these toxins are *Microcystis*, *Planktothrix* and *Anabaena*. Microcystins usually occur within the cells; substantial amounts are released to the surrounding water only in situations of cell rupture (i.e., lysis).

Provisional guideline value	0.001 mg/litre (for total microcystin-LR, free plus cell-bound) The guideline value is provisional, as it covers only microcystin-LR, the database is limited and new data for the toxicity of cyanobacterial toxins are being generated.
TDI	0.04 µg/kg of body weight, based on liver pathology observed in a 13-week study in mice and applying an uncertainty factor of 1000, taking into consideration limitations in the database, in particular lack of data on chronic toxicity and carcinogenicity
Limit of detection	0.1–1 µg/litre by HPLC following extraction of cells with 75% aqueous methanol or following concentration of microcystins from liquid samples on C-18; will allow differentiation between variants where standards are available. 0.1–0.5 µg/litre by commercially available immunoassay kits (ELISA) for microcystins dissolved in water or in aqueous extracts of cells; will detect most microcystins. These are less precise in quantification than HPLC, but useful for screening. 0.5–1.5 µg/litre by protein phosphatase assay for microcystins dissolved in water or in aqueous extracts of cells; will detect all microcystins. This assay is less precise in quantification and identification than HPLC, but useful for screening.
Monitoring	The preferred approach is visual monitoring (including microscopy for potentially microcystin-containing genera) of source water for evidence of increasing cyanobacterial cell density (blooms) or bloom-forming potential, and increased vigilance where such events occur. Chemical monitoring of microcystins is not the preferred focus.
Prevention and treatment	Actions to decrease the probability of bloom occurrence include catchment and source water management, such as reducing nutrient loading or changing reservoir stratification and mixing. Treatment effective for the removal of cyanobacteria includes filtration to remove intact cells. Treatment effective against free microcystins in water (as well as most other free cyanotoxins) includes oxidation through ozone or chlorine at sufficient concentrations and contact times, as well as GAC and some PAC applications.

Guideline derivation	
● allocation to water	80% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	While guideline values are derived where sufficient data exist, they are intended to inform the interpretation of monitoring data and not to indicate that there is a requirement for routine monitoring by chemical analysis.

Toxicological review

Microcystin-LR is a potent inhibitor of eukaryotic protein serine/threonine phosphatases 1 and 2A. The primary target for microcystin toxicity is the liver, as microcystins cross cell membranes chiefly through the bile acid transporter. Guideline derivation was based on an oral 13-week study with mice, supported by an oral 44-day study with pigs. A large number of poisonings of livestock and wildlife have been recorded. Evidence of tumour promotion has been published.

History of guideline development

Cyanobacterial toxins were not evaluated in the 1958, 1963 and 1971 WHO *International Standards for Drinking-water* or in the first two editions of the *Guidelines for Drinking-water Quality*, published in 1984 and 1993. In the addendum to the second edition of the Guidelines, published in 1998, it was concluded that there were insufficient data to allow a guideline value to be derived for any cyanobacterial toxins other than microcystin-LR. A health-based guideline value for total microcystin-LR (free plus cell-bound) of 0.001 mg/litre was derived, assuming significant exposure from drinking-water. The guideline value was designated as provisional, as it covers only microcystin-LR, the database is limited and new data for the toxicity of cyanobacterial toxins are being generated.

Assessment date

The risk assessment was conducted in 2003.

Principal references

- Chorus I, Bartram J, eds. (1999) *Toxic cyanobacteria in water: A guide to their public health consequences, monitoring and management*. Published by E & FN Spon, London, on behalf of the World Health Organization, Geneva.
- WHO (2003) *Cyanobacterial toxins: Microcystin-LR in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/57).

12.87 Molinate

Molinate (CAS No. 2212-67-1) is a herbicide used to control broad-leaved and grassy weeds in rice. The available data suggest that groundwater pollution by molinate is

restricted to some rice-growing regions. Data on the occurrence of molinate in the environment are limited. Molinate is of low persistence in water and soil, with a half-life of about 5 days.

Guideline value	0.006 mg/litre
Occurrence	Concentrations in water rarely exceed 1 µg/litre.
TDI	2 µg/kg of body weight, based on a NOAEL for reproductive toxicity in the rat of 0.2 mg/kg of body weight, with an uncertainty factor of 100 (for inter- and intraspecies variation)
Limit of detection	0.01 µg/litre by GC/MS
Treatment achievability	0.001 mg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

On the basis of the limited information available, molinate does not seem to be carcinogenic or mutagenic in animals. Evidence suggests that impairment of the reproductive performance of the male rat represents the most sensitive indicator of molinate exposure. However, epidemiological data based on the examination of workers involved in molinate production do not indicate any effect on human fertility.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to molinate, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Molinate was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines established a health-based guideline value of 0.006 mg/litre for molinate in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Molinate in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/40).

12.88 Molybdenum

Molybdenum is found naturally in soil and is used in the manufacture of special steels and in the production of tungsten and pigments, and molybdenum compounds are used as lubricant additives and in agriculture to prevent molybdenum deficiency in crops.

Guideline value	0.07 mg/litre
Occurrence	Concentrations in drinking-water are usually less than 0.01 mg/litre, although concentrations as high as 200 µg/litre have been reported in areas near mining sites.
NOAEL	0.2 mg/litre in a 2-year study of humans exposed through their drinking-water, using an uncertainty factor of 3 for intraspecies variation (because molybdenum is an essential element)
Limit of detection	0.25 µg/litre by graphite furnace AAS; 2 µg/litre by ICP/AES
Treatment achievability	Molybdenum is not removed from drinking-water.
Additional comments	The guideline value is within the range of that derived on the basis of results of toxicological studies in animal species and is consistent with the essential daily requirement.

Toxicological review

Molybdenum is considered to be an essential element, with an estimated daily requirement of 0.1–0.3 mg for adults. No data are available on the carcinogenicity of molybdenum by the oral route. Additional toxicological information is needed on the impact of molybdenum on bottle-fed infants.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to molybdenum. The 1971 International Standards stated that molybdenum should be controlled in drinking-water, but that insufficient information was available to enable a tentative limit to be established. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was concluded that no action was required for molybdenum. The 1993 Guidelines proposed a health-based guideline value of 0.07 mg/litre for molybdenum based on a 2-year study of humans exposed through their drinking-water. This value is within the range of that derived on the basis of results of toxicological studies in animal species and is consistent with the essential daily requirement.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Molybdenum in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/11).

12.89 Monochloramine

Mono-, di- and trichloramines are considered by-products of drinking-water chlorination, being formed when ammonia is added to chlorinated water. Monochloramine may also be added to maintain residual disinfection activity in potable water distribution systems. The use of chloramines for disinfection instead of chlorine reduces the formation of THMs in drinking-water supplies. However, formation of other by-products, such as halo ketones, chloropicrin, cyanogen chloride, haloacetic acids, haloacetonitriles, aldehydes and chlorophenols, has been reported. Monochloramine is recognized as a less effective disinfectant than chlorine. Only monochloramine, the most abundant chloramine, is considered here, as it has been the most extensively studied.

Guideline value	3 mg/litre
Occurrence	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.
TDI	94 µg/kg of body weight, based on a NOAEL of 9.4 mg/kg of body weight per day, the highest dose administered to male rats in a 2-year NTP drinking-water study (although mean body weights of rats given the highest dose were lower than those of their respective control groups, it is probable that the lower body weights were caused by the unpalatability of the drinking-water)
Limit of detection	10 µg/litre by colorimetric methods
Treatment achievability	It is possible to reduce the concentration of chloramine effectively to zero (<0.1 mg/litre) by reduction; however, it is normal practice to supply water with a chloramine residual of a few tenths of a milligram per litre to act as a preservative during distribution.
Guideline derivation	
● allocation to water	100% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	<ul style="list-style-type: none"> ● 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. ● Most individuals are able to taste chloramines at concentrations below 5 mg/litre, and some at levels as low as 0.3 mg/litre.

Toxicological review

Although monochloramine has been shown to be mutagenic in some *in vitro* studies, it has not been found to be genotoxic *in vivo*. IARC has classified chloramine in Group 3, and the US EPA has classified monochloramine in group D (not classifiable as to human carcinogenicity, as there is inadequate human and animal evidence). In the NTP bioassay in two species, the incidence of mononuclear cell leukaemias in female F344/N rats was increased, but no other increases in tumour incidence were observed. IPCS (2000) did not consider that the increase in mononuclear cell leukaemia was treatment-related.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to chloramines. The 1993 Guidelines established a health-based guideline value of 3 mg/litre for monochloramine in drinking-water. Available data were insufficient for the establishment of guideline values for dichloramine and trichloramine. It was noted that the odour thresholds for dichloramine and trichloramine are much lower than that for monochloramine.

Assessment date

The risk assessment was conducted in 2003.

Principal references

IPCS (2000) *Disinfectants and disinfectant by-products*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 216).

WHO (2003) *Monochloramine in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/83).

12.90 Monochloroacetic acid

Chlorinated acetic acids are formed from organic material during water chlorination.

12. CHEMICAL FACT SHEETS

Guideline value	0.02 mg/litre
Occurrence	Present in surface water-derived drinking-water at <2–82 µg/litre (mean 2.1 µg/litre)
TDI	3.5 µg/kg of body weight, based on a LOAEL of 3.5 mg/kg of body weight per day from a study in which increased absolute and relative spleen weights were observed in male rats exposed to monochloroacetic acid in drinking-water for 2 years, and using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for use of a minimal LOAEL instead of a NOAEL and database deficiencies, including the lack of a multigeneration reproductive toxicity study)
Limit of detection	2 µg/litre by GC with ECD; 5 µg/litre by GC/MS
Treatment achievability	No information available
Guideline derivation	
● allocation to water	20% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

No evidence of carcinogenicity of monochloroacetate was found in 2-year gavage bioassays with rats and mice. Monochloroacetate has given mixed results in a limited number of mutagenicity assays and has been negative for clastogenicity in genotoxicity studies. IARC has not classified the carcinogenicity of monochloroacetic acid.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to monochloroacetic acid. The 1993 Guidelines did not establish a guideline value for monochloroacetic acid, as available toxicity data were considered insufficient.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Monochloroacetic acid in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/85).

12.91 Monochlorobenzene

Releases of monochlorobenzene (MCB) to the environment are thought to be mainly due to volatilization losses associated with its use as a solvent in pesticide formulations, as a degreasing agent and from other industrial applications. MCB has been

detected in surface water, groundwater and drinking-water; mean concentrations were less than 1 µg/litre in some potable water sources (maximum 5 µg/litre) in Canada. The major source of human exposure is probably air.

MCB is of low acute toxicity. Oral exposure to high doses of MCB affects mainly the liver, kidneys and haematopoietic system. There is limited evidence of carcinogenicity in male rats, with high doses increasing the occurrence of neoplastic nodules in the liver. The majority of evidence suggests that MCB is not mutagenic; although it binds to DNA *in vivo*, the level of binding is low.

A health-based value of 300 µg/litre can be calculated for MCB on the basis of a TDI of 85.7 µg/kg of body weight, based on neoplastic nodules identified in a 2-year rat study with dosing by gavage, and taking into consideration the limited evidence of carcinogenicity. However, because MCB occurs at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a guideline value. It should also be noted that the health-based value far exceeds the lowest reported taste and odour threshold for MCB in water.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to MCB. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline value for chlorobenzene was recommended after a detailed evaluation of the compound. Following consideration of the calculated toxicological limit for drinking-water of 0.005–0.05 mg/litre based on a tentative ADI and the fact that the threshold odour concentration of MCB in water is 0.03 mg/litre, no guideline value was recommended, and 0.003 mg/litre was recommended to avoid taste and odour problems in drinking-water. The 1993 Guidelines proposed a health-based guideline value of 0.3 mg/litre for MCB, noting that this value far exceeds the lowest reported taste and odour threshold for MCB in water (0.01 mg/litre).

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Monochlorobenzene in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/107).

12.92 MX

MX, which is the common name for 3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone, is formed by the reaction of chlorine with complex organic matter in drinking-water. 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. Five drinking-water samples from different Japanese cities contained MX at concentrations ranging from <3 to 9 ng/litre.

MX is a potent mutagen in bacteria and in cells *in vitro* and has undergone a life-time study in rats in which some tumorigenic responses were observed. These data indicate that MX induces thyroid and bile duct tumours. IARC has classified MX in Group 2B on the basis of rat tumorigenicity and its strong mutagenicity.

A health-based value of 1.8 µg/litre can be calculated for MX on the basis of the increase in cholangiomas and cholangiocarcinomas in female rats using the linearized multistage model (without a body surface area correction). However, this is significantly above the concentrations that would be found in drinking-water, and, in view of the analytical difficulties in measuring this compound at such low concentrations, it is considered unnecessary to propose a formal guideline value for MX in drinking-water.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to MX. The 1993 Guidelines concluded that available data were inadequate to permit a guideline value for MX to be established.

Assessment date

The risk assessment was conducted in 2003.

Principal references

IPCS (2000) *Disinfectants and disinfectant by-products*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 216).

WHO (2003) *MX in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/108).

12.93 Nickel

Nickel is used mainly in the production of stainless steel and nickel alloys. Food is the dominant source of nickel exposure in the non-smoking, non-occupationally exposed population; water is generally a minor contributor to the total daily oral intake. However, where there is heavy pollution, where there are areas in which nickel that naturally occurs in groundwater is mobilized or where there is use of certain types of kettles, of non-resistant material in wells or of water that has come into contact with nickel- or chromium-plated taps, the nickel contribution from water may be significant.

GUIDELINES FOR DRINKING-WATER QUALITY

Guideline value	0.07 mg/litre
Occurrence	The concentration of nickel in drinking-water is normally less than 0.02 mg/litre, although nickel released from taps and fittings may contribute up to 1 mg/litre. In special cases of release from natural or industrial nickel deposits in the ground, the nickel concentrations in drinking-water may be higher.
TDI	12 µg/kg of body weight, derived from a LOAEL established after oral provocation of fasted patients with an empty stomach
Limit of detection	0.1 µg/litre by ICP-MS; 0.5 µg/litre by FAAS; 10 µg/litre by ICP-AES
Treatment achievability	20 µg/litre should be achievable by conventional treatment, e.g., coagulation. Where naturally occurring nickel is mobilized in groundwater, removal is by ion exchange or adsorption. Where nickel leaches from alloys in contact with drinking-water or from chromium- or nickel-plated taps, control is by appropriate control of materials in contact with the drinking-water and flushing taps before using the water.
Guideline derivation	
● allocation to water	20% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	<ul style="list-style-type: none"> ● Although the guideline value is close to the acute LOAEL, the LOAEL is based on total exposure from drinking-water, and absorption from drinking-water on an empty stomach is 10- to 40-fold higher than absorption from food. Deriving the total acceptable intake for oral challenge from studies using drinking-water on an empty stomach in fasted patients can, therefore, be considered a worst-case scenario. ● A general toxicity value of 130 µg/litre could be determined from a well conducted two-generation study in rats. However, this general toxicity value may not be sufficiently protective of individuals sensitized to nickel, for whom a sufficiently high oral challenge has been shown to elicit an eczematous reaction.

Toxicological review

IARC concluded that inhaled nickel compounds are carcinogenic to humans (Group 1) and that metallic nickel is possibly carcinogenic (Group 2B). However, there is a lack of evidence of a carcinogenic risk from oral exposure to nickel. In a well conducted two-generation reproductive study in rats administered nickel by gavage, a clear NOEL was observed for adult rats and their offspring for all the end-points studied, including integrity and performance of male and female reproductive systems, growth and development of offspring and post-implantation/perinatal lethality. Allergic contact dermatitis is the most prevalent effect of nickel in the general population.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to nickel. In the first edition of the *Guidelines for Drinking-water Quality*, pub-

lished in 1984, it was concluded that the toxicological data available indicate that a guideline value for nickel in drinking-water was not required. A health-based guideline value of 0.02 mg/litre was derived in the second edition of the Guidelines, published in 1993, which should provide sufficient protection for individuals who are sensitive to nickel. This guideline value was maintained in the addendum to the second edition, published in 1998, because, on the basis of the available data, it was considered to provide sufficient protection for individuals who are sensitive to nickel. However, the guideline value was designated as provisional owing to uncertainties about the effect level for perinatal mortality. This value was brought forward to the third edition.

Assessment date

The risk assessment was conducted in 2004.

Principal reference

WHO (2005) *Nickel in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/55).

12.94 Nitrate and nitrite¹

Nitrate (NO₃) is found naturally in the environment and is an important plant nutrient. It is present at varying concentrations in all plants and is a part of the nitrogen cycle. Nitrite (NO₂) is not usually present in significant concentrations except in a reducing environment, since nitrate is the most stable oxidation state. It can be formed by the microbial reduction of nitrate. Nitrite can also be formed chemically in distribution pipes by *Nitrosomonas* bacteria during stagnation of nitrate-containing and oxygen-poor drinking-water in galvanized steel pipes or if chloramination is used to provide a residual disinfectant.

Nitrate can reach both surface water and groundwater as a consequence of agricultural activity (including excess application of inorganic nitrogenous fertilizers and manures), from wastewater disposal and from oxidation of nitrogenous waste products in human and animal excreta, including septic tanks. Surface water nitrate concentrations can change rapidly owing to surface runoff of fertilizer, uptake by phytoplankton and denitrification by bacteria, but groundwater concentrations generally show relatively slow changes. Some groundwaters may also have nitrate contamination as a consequence of leaching from natural vegetation.

In general, the most important source of human exposure to nitrate and nitrite is through vegetables (nitrite and nitrate) and through meat in the diet (nitrite is used as a preservative in many cured meats). In some circumstances, however, drinking-

¹ As nitrate is one of the chemicals of greatest health concern in some natural waters, the chemical fact sheet on nitrate and nitrite has been expanded.

12. CHEMICAL FACT SHEETS

water can make a significant contribution to nitrate and, occasionally, nitrite intake. In the case of bottle-fed infants, drinking-water can be the major external source of exposure to nitrate and nitrite.

Guideline value for nitrate	50 mg/litre to protect against methaemoglobinaemia in bottle-fed infants (short-term exposure)
Guideline value / Provisional guideline value for nitrite	<ul style="list-style-type: none"> • 3 mg/litre for methaemoglobinaemia in infants (short-term exposure) • 0.2 mg/litre (provisional) (long-term exposure) <p>The guideline value for chronic effects of nitrite is considered provisional owing to uncertainty surrounding the susceptibility of humans compared with animals.</p>
Guideline value for combined nitrate plus nitrite	The sum of the ratios of the concentrations of each to its guideline value should not exceed 1.
Occurrence	In most countries, nitrate levels in drinking-water derived from surface water do not exceed 10 mg/litre, although nitrate levels in well water often exceed 50 mg/litre; nitrite levels are normally lower, less than a few milligrams per litre.
Basis of guideline derivation	<ul style="list-style-type: none"> • Nitrate (bottle-fed infants): in epidemiological studies, methaemoglobinaemia was not reported in infants in areas where drinking-water consistently contained less than 50 mg of nitrate per litre • Nitrite (bottle-fed infants): application of body weight of 5 kg for an infant and drinking-water consumption of 0.75 litre to lowest level of toxic dose range, 0.4 mg/kg of body weight • Nitrite (long-term exposure): based on allocation to drinking-water of 10% of JECFA ADI of 0.07 mg/kg of body weight per day, based on nitrite-induced morphological changes in the adrenals, heart and lungs in laboratory animal studies
Limit of detection	0.1 mg/litre (nitrate) and 0.05 mg/litre (nitrite) by LC; 0.01–1 mg/litre (nitrate) by spectrometric techniques; 0.005–0.01 mg/litre (nitrite) by a molecular absorption spectrometric method; 22 µg/litre (nitrate) and 35 µg/litre (nitrite) by IC
Treatment achievability	<ul style="list-style-type: none"> • Nitrate: 5 mg/litre or lower should be achievable using biological denitrification (surface waters) or ion exchange (groundwaters) • Nitrite: 0.1 mg/litre should be achievable using chlorination (to form nitrate)
Additional comments	<ul style="list-style-type: none"> • Nitrite can occur in distribution at higher concentrations when chloramination is used, but the occurrence is almost invariably sporadic. Methaemo-globinaemia is therefore the most important consideration, and the guideline derived for protection against methaemoglobinaemia would be the most appropriate under these circumstances, allowing for any nitrate that may also be present. • Methaemoglobinaemia in infants appears to be associated with simultaneous exposure to microbial contaminants. Authorities should therefore be all the more vigilant that water to be used for bottle-fed infants is microbiologically safe when nitrate is present at concentrations near the guideline value

- All water systems that practise chloramination should closely and regularly monitor their systems to verify disinfectant levels, microbiological quality and nitrite levels. If nitrification is detected (e.g., reduced disinfectant residuals and increased nitrite levels), steps should be taken to modify the treatment train or water chemistry in order to maintain a safe water quality. Efficient disinfection must never be compromised.
 - The occurrence of nitrite in distribution as a consequence of chloramine use will be intermittent, and average exposures over time should not exceed the provisional guideline value.
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Toxicological review

Absorption of nitrate ingested from vegetables, meat or water is rapid and in excess of 90%, and final excretion is in the urine. In humans, about 25% of ingested nitrate is recirculated in saliva, of which about 20% is converted to nitrite by the action of bacteria in the mouth. There is also the potential for endogenous formation of nitrate from nitric oxide and protein breakdown. In normal healthy adults, this endogenous synthesis leads to the excretion of about 62 mg of nitrate ion per day in the urine. Endogenous formation of nitrate can be significantly increased in the presence of infections, particularly gastrointestinal infections. When nitrate intake is low, endogenous formation may be the major source of nitrate in the body. Nitrate metabolism is different in humans and rats, since rats actively secrete virtually no nitrate in their saliva.

Significant bacterial reduction of nitrate to nitrite does not normally take place in the stomach, except in individuals with low gastric acidity or with gastrointestinal infections. These can include individuals using antacids, particularly those that block acid secretion, and potentially bottle-fed infants (due to relatively higher stomach pH), although there is some uncertainty regarding the latter.

In humans, methaemoglobinaemia forms as a consequence of the reaction of nitrite with haemoglobin in the red blood cells to form methaemoglobin, which binds oxygen tightly and does not release it, so blocking oxygen transport. Although most absorbed nitrite is oxidized to nitrate in the blood, residual nitrite can react with haemoglobin. High levels of methaemoglobin (greater than 10%) formation can give rise to cyanosis, referred to as blue-baby syndrome. Although clinically significant methaemoglobinaemia can occur as a result of extremely high nitrate intake in adults and children, the most familiar situation is its occurrence in bottle-fed infants. This was considered to be primarily a consequence of high levels of nitrate in water, although there have been cases of methaemoglobinaemia in weaned infants associated with high nitrate intake from vegetables. Bottle-fed infants are considered to be at greater risk because the intake of water in relation to body weight is high and, in infants, the development of repair enzymes is limited. In clinical epidemiological studies of methaemoglobinaemia and subclinical increases in methaemoglobin associated with drinking-water nitrate, 97% of cases occurred at concentrations in excess

of 44.3 mg/litre, with clinical symptoms associated with the higher concentrations. The affected individuals were almost exclusively under 3 months of age.

While drinking-water nitrate may be an important risk factor for bottle-fed infants, there is good evidence that the risk of methaemoglobinaemia is primarily increased in the presence of simultaneous gastrointestinal infections, which increase endogenous nitrate formation, may increase nitrate reduction to nitrite and may also increase the intake of water in combatting dehydration. Cases have been described in which gastrointestinal infection seems to have been the primary cause of methaemoglobinaemia. Most cases of methaemoglobinaemia reported in the literature are associated with contaminated private wells that also have a high probability of microbial contamination and predominantly when the drinking-water is anaerobic, which should not occur if it is properly disinfected.

Nitrite can react with nitrosatable compounds, primarily amines, in the body to form *N*-nitroso compounds. A number of these are considered to be carcinogenic to humans, whereas others, such as *N*-nitrosoproline, are not. Several studies have been carried out on the formation of *N*-nitroso compounds in relation to nitrate intake in humans, but there is large variation in the intake of nitrosatable compounds and in gastric physiology. Higher mean levels of *N*-nitroso compounds, along with high nitrate levels, have been found in the gastric juice of individuals who are achlorhydric (very low levels of hydrochloric acid in the stomach). However, other studies have been largely inconclusive, and there appears to be no clear relationship with drinking-water nitrate compared with overall nitrate intake. A number of dietary antioxidant components, such as moderate consumption of ascorbic acid and green tea, appear to reduce endogenous *N*-nitrosamine formation.

A significant number of epidemiological studies have been carried out on the association of nitrate intake with primarily gastric cancers. Although the epidemiological data are considered to be inadequate to allow definitive conclusions to be drawn regarding all cancers, there is no convincing evidence of a causal association with any cancer site. The weight of evidence indicates that there is unlikely to be a causal association between gastric cancer and nitrate in drinking-water.

There have been suggestions that nitrate in drinking-water could be associated with congenital malformations, but the overall weight of evidence does not support this.

Nitrate appears to competitively inhibit iodine uptake, with the potential for an adverse effect on the thyroid; however, this would be an issue only under circumstances of very high nitrate intake and simultaneous iodine deficiency, which appears to be the most important factor.

There have been suggestions of an association between nitrate in drinking-water and the incidence of childhood diabetes mellitus. However, subsequent studies have not found a significant relationship, and no mechanism was identified.

Nitrate may have a role in protecting the gastrointestinal tract against a variety of gastrointestinal pathogens, since nitrous oxide and acidified nitrite have antibacterial properties. There may, therefore, be a benefit from nitrate uptake, but endogenous

synthesis probably provides sufficiently high levels of nitrate for biocidal activity, and there remains a need to balance the potential risks with the potential benefits.

In some studies in rats treated with high doses of nitrite, a dose-related hypertrophy of the zona glomerulosa of the adrenal was seen; one strain of rats appeared to be more sensitive than others. However, this minimal hyperplasia was considered to be due to physiological adaptation to small fluctuations in blood pressure in response to high nitrite doses.

Nitrate is not carcinogenic in laboratory animals. Nitrite has been frequently studied, and there have been suggestions of carcinogenic activity, but only at very high doses. Results from some carcinogenicity bioassays with nitrite were not conclusive. The most recent long-term studies have shown only equivocal evidence of carcinogenicity in the forestomach of female mice, but not in rats or male mice. In view of the lack of evidence for genotoxicity, this led to the conclusion that sodium nitrite was not carcinogenic in mice and rats. In addition, since humans do not possess a forestomach and the doses were high, the significance of these data for humans is very doubtful.

The guideline value for nitrate of 50 mg/litre as nitrate is based on epidemiological evidence for methaemoglobinaemia in infants, which results from short-term exposure and is protective for bottle-fed infants and, consequently, other parts of the population. This outcome is complicated by the presence of microbial contamination and subsequent gastrointestinal infection, which can increase the risk for this group significantly. Authorities should therefore be all the more vigilant that water to be used for bottle-fed infants is microbiologically safe when nitrate is present at concentrations near the guideline value. However, the water must also be known to be microbiologically safe. The latter is a minor modification of previous guidance to give greater emphasis to the role of microbiological quality.

The guideline for nitrite of 3 mg/litre is based on human data showing that doses of nitrite that cause methaemoglobinaemia in infants range from 0.4 to more than 200 mg/kg of body weight. By applying the lowest level of the range (0.4 mg/kg of body weight), a body weight of 5 kg for an infant and a drinking-water consumption of 0.75 litre, a guideline value of 3 mg/litre (rounded figure) can be derived.

Because of the possibility of the simultaneous occurrence of nitrate and nitrite in drinking-water, the sum of the ratios of the concentration (C) of each to its guideline value (GV) should not exceed one, i.e.,

$$\frac{C_{\text{nitrate}}}{GV_{\text{nitrate}}} + \frac{C_{\text{nitrite}}}{GV_{\text{nitrite}}} \leq 1$$

For chronic exposure, JECFA has proposed an ADI for nitrate of 0–3.7 mg/kg of body weight and an ADI of 0–0.07 mg/kg of body weight for nitrite, expressed as nitrite ion. The value for nitrate is based on a NOEL of 370 mg/kg of body weight per day in laboratory animal studies; in view of the known interspecies variation in nitrate/nitrite metabolism, however, it was not considered appropriate at this time to

use this in the risk assessment for humans. The ADI for nitrite is based on effects on heart and lung in a 2-year study in rats with a safety factor of 100. In view of the unusual findings in animals following chronic exposure to nitrite, it was considered prudent to also consider a guideline value for nitrite associated with chronic exposure. Using JECFA's ADI of 0–0.07 mg/kg of body weight, assuming a 60-kg adult ingesting 2 litres of drinking-water per day, and allocating 10% of the ADI to drinking-water, a guideline value of 0.2 mg of nitrite ion per litre (rounded figure) can be calculated. However, owing to the uncertainty surrounding the susceptibility of humans compared with animals, this guideline value should be considered provisional.

Practical considerations

The most appropriate means of controlling nitrate concentrations, particularly in groundwater, is the prevention of contamination (Schmoll et al., 2006). This may take the form of appropriate management of agricultural practices, the careful siting of pit latrines and septic tanks, sewer leakage control, as well as management of fertilizer and manure application and storage of animal manures. It may also take the form of denitrification of wastewater effluents.

Methaemoglobinaemia has most frequently been associated with private wells. It is particularly important to ensure that septic tanks and pit latrines are not sited near a well or where a well is to be dug and to ensure that animal manure is kept at a sufficient distance to ensure that runoff cannot enter the well or the ground near the well. It is particularly important that the household use of manures and fertilizers on small plots near wells should be managed with care to avoid potential contamination. The well should be sufficiently protected to prevent runoff from entering the well. Where there are elevated concentrations of nitrate or where inspection of the well indicated that there are sources of nitrate close by that could be causing contamination, particularly where there are also indications that microbiological quality might also be poor, a number of actions can be taken. Water should be boiled or disinfected by an appropriate means before consumption. Where alternative supplies are available for bottle-fed infants, these can be used, taking care to ensure that they are microbiologically safe. Steps should then be taken to protect the well and ensure that sources of both nitrate and microbial contamination are removed from the vicinity of the well.

In areas where household wells are common, health authorities may wish to take a number of steps to ensure that nitrate contamination is not or does not become a problem. Such steps could include targeting mothers, particularly expectant mothers, with appropriate information about water safety, assisting with visual inspection of wells to determine whether a problem may exist, providing testing facilities where a problem is suspected, providing guidance on disinfecting water or where nitrate levels are particularly high, providing bottled water from safe sources or providing advice as to where such water can be obtained.

With regard to piped supplies, where nitrate is present, the first potential approach to treatment of drinking-water supplies, if source substitution is not feasible, is to dilute the contaminated water with a low-nitrate source. Where blending is not feasible, a number of treatment techniques are available for drinking-water. The first is disinfection, which may serve to oxidize nitrite to the less toxic nitrate as well as minimize the pathogenic and non-pathogenic reducing bacterial population in the water. Nitrate removal methods include ion exchange (normally for groundwaters) and biological denitrification (normally for surface waters). However, there are disadvantages associated with both approaches, including the need for regeneration and disposal of spent regenerant with ion exchange, the complexities of operation and the potential for microbial and carbon feed contamination of the final water with biological denitrification.

Care should be taken with the use of chloramination for providing a residual disinfectant in the distribution system. It is important to manage this to minimize nitrite formation, either in the main distribution system or in the distribution systems of buildings where chloramines are used to control *Legionella*.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* referred to nitrates, stating that the ingestion of water containing nitrates in excess of 50–100 mg/litre (as nitrate) may give rise to methaemoglobinaemia in infants under 1 year of age. In the 1963 *International Standards*, this value was lowered to 45 mg/litre (as nitrate), which was retained in the 1971 *International Standards*. The 1971 *International Standards* first mentioned concern over the possibility of nitrosamine formation *in vivo*; as nitrosamines are a possible hazard to human health, the 1971 *Standards* stated that it may eventually become necessary to reduce the level of nitrates in water if it is found that this source makes a significant contribution to the hazard to human health arising from nitrosamines. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 10 mg/litre for nitrate-nitrogen was recommended. It was also recommended that the guideline value for nitrite must be correspondingly lower than that for nitrate, and it was noted that the nitrite-nitrogen level should be considerably lower than 1 mg/litre where drinking-water is correctly treated. The 1993 *Guidelines* concluded that extensive epidemiological data support the current guideline value for nitrate-nitrogen of 10 mg/litre, but stated that this value should be expressed not on the basis of nitrate-nitrogen but on the basis of nitrate itself, which is the chemical entity of concern to health. The guideline value for nitrate is therefore 50 mg/litre. This guideline value for methaemoglobinaemia in infants, an acute effect, was confirmed in the addendum to the *Guidelines*, published in 1998. It was also concluded in the 1993 *Guidelines* that a guideline value for nitrite should be proposed, although no suitable animal studies of methaemoglobinaemia were available. A provisional guideline value for nitrite of 3 mg/litre was therefore proposed by accepting a relative potency for nitrite and nitrate with respect to methaemo-

globin formation of 10:1 (on a molar basis). In the addendum to the Guidelines, published in 1998, it was concluded that human data on nitrite reviewed by JECFA supported the guideline value of 3 mg/litre, based on induction of methaemoglobinaemia in infants, and the guideline value was no longer designated as provisional. In addition, a guideline value of 0.2 mg/litre for nitrate ion associated with long-term exposure was derived in the addendum to the Guidelines, based on JECFA's ADI. However, because of the uncertainty surrounding the relevance of the observed adverse health effects for humans and the susceptibility of humans compared with animals, this guideline value was considered provisional. Because of the possibility of simultaneous occurrence of nitrite and nitrate in drinking-water, it was recommended in the 1993 and 1998 Guidelines that the sum of the ratios of the concentration of each to its guideline value should not exceed 1. These guideline values were retained in the third edition of the Guidelines, published in 2004.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to the third edition of the *Guidelines for Drinking-water Quality*, published in 2004. An expanded summary statement based on the risk assessment was prepared for the second addendum to the third edition, published in 2007.

Principal references

- FAO/WHO (2002) *Evaluation of certain food additives. Fifty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives*. Geneva, World Health Organization (WHO Technical Report Series No. 913; http://whqlibdoc.who.int/trs/WHO_TRS_913.pdf).
- FAO/WHO (2003) Nitrite (and potential endogenous formation of *N*-nitroso compounds). In: *Safety evaluation of certain food additives and contaminants*. Geneva, World Health Organization, Joint FAO/WHO Expert Committee on Food Additives (WHO Food Additives Series, No. 50; <http://www.inchem.org/documents/jecfa/jecmono/v50je05.htm>).
- FAO/WHO (2003) Nitrate (and potential endogenous formation of *N*-nitroso compounds). In: *Safety evaluation of certain food additives and contaminants*. Geneva, World Health Organization, Joint FAO/WHO Expert Committee on Food Additives (WHO Food Additives Series, No. 50; <http://www.inchem.org/documents/jecfa/jecmono/v50je06.htm>).
- Schmoll O et al. (2006) *Protecting groundwater for health. Managing the quality of drinking-water sources*. London, IWA Publishing, on behalf of the World Health Organization.
- WHO (2007) *Nitrate and nitrite in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/HSE/AMR/07.01/16).

12.95 Nitrilotriacetic acid (NTA)

Nitrilotriacetic acid (NTA) is used primarily in laundry detergents as a replacement for phosphates and in the treatment of boiler water to prevent accumulation of mineral scale.

Guideline value	0.2 mg/litre
Occurrence	Concentrations in drinking-water usually do not exceed a few micrograms per litre, although concentrations as high as 35 µg/litre have been measured.
TDI	10 µg/kg of body weight, based on nephritis and nephrosis in a 2-year study in rats and using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for carcinogenic potential at high doses)
Limit of detection	0.2 µg/litre using GC with a nitrogen-specific detector
Treatment achievability	No data available
Guideline derivation	
• allocation to water	50% of TDI
• weight	60-kg adult
• consumption	2 litres/day

Toxicological review

NTA is not metabolized in animals and is rapidly eliminated, although some may be briefly retained in bone. It is of low acute toxicity to animals, but it has been shown to produce kidney tumours in rodents following long-term exposure to doses higher than those required to produce nephrotoxicity. IARC has placed NTA in Group 2B. It is not genotoxic, and the reported induction of tumours is believed to be due to cytotoxicity resulting from the chelation of divalent cations such as zinc and calcium in the urinary tract, leading to the development of hyperplasia and subsequently neoplasia.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to NTA. The 1971 *International Standards* stated that NTA should be controlled in drinking-water, but that insufficient information was available to enable a tentative limit to be established. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was determined that no further action on NTA was required. A health-based guideline value of 0.2 mg/litre was established for NTA in the 1993 *Guidelines*.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Nitritotriacetic acid in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/30).

12.95(a) N-Nitrosodimethylamine (NDMA)

N-Nitrosodimethylamine, or NDMA, can occur in drinking-water through the degradation of dimethylhydrazine (a component of rocket fuel) as well as from several other industrial processes. It is also a contaminant of certain pesticides. NDMA has recently been identified as a disinfection by-product of chloramination (by the reaction of monochloramine with dimethylamine, a ubiquitous component of waters impacted by wastewater discharges) and, to some extent, chlorination. NDMA can also be formed as a by-product of anion-exchange treatment of water.

12. CHEMICAL FACT SHEETS

Guideline value	0.0001 mg/litre (0.1 µg/litre)
Occurrence	Where chloramination is used, distribution system samples can have much higher levels of NDMA than the finished water at the treatment plant. Levels as high as 0.16 µg/litre have been measured in the distribution system, but concentrations in water at the treatment plant are generally less than 0.01 µg/litre.
Basis of guideline derivation	Hepatic biliary cystadenomas in female rats, the most sensitive carcinogenic end-point, observed in a drinking-water study, using a multistage model
Limit of detection	0.028 ng/litre by capillary column GC and chemical ionization tandem MS; 0.4 ng/litre by capillary column GC and high-resolution MS; 0.7–1.6 ng/litre by GC/MS and ammonia positive chemical ionization detection.
Treatment achievability	The most common process for NDMA removal is UV irradiation. A concentration below 0.005 µg/litre should be achievable by UV irradiation provided that the water is not grossly contaminated. NDMA is not removable by air stripping, activated carbon adsorption, reverse osmosis or biodegradation.
Additional comments	Potential methods for reducing the formation of NDMA during disinfection include avoiding the use of chloramination, use of breakpoint chlorination and removal of ammonia prior to chlorination.

Toxicological review

There is conclusive evidence that NDMA is a potent carcinogen in experimental animals by several routes of exposure, including through ingestion of drinking-water. NDMA has been classified by IARC as probably carcinogenic to humans. The mechanism by which NDMA produces cancer is well understood to involve biotransformation by liver microsomal enzymes, generating the methyldiazonium ion. This reactive metabolite forms DNA adducts, with most evidence pointing to O⁶-methylguanine as the likely proximal carcinogenic agent. As a consequence of the clear evidence of carcinogenicity, there have been few studies of other possible toxic end-points.

There is also ample evidence that NDMA is genotoxic both *in vivo* and *in vitro*. Activation by liver microsomal S9 fractions is necessary for a positive *in vitro* result. The recent observation that human S9 fractions are much more active in promoting genotoxicity in the Ames test than rat S9 fractions suggests that humans may be especially sensitive to the carcinogenicity of NDMA.

Although there have been several case-control studies and one cohort study of NDMA in humans, none of them can be used to derive a quantitative risk of cancer. The results are supportive of the assumption that NDMA consumption is positively associated with either gastric or colorectal cancer. However, none of the studies focused on drinking-water as the route of exposure; instead, they used estimations of total dietary intake of NDMA.

History of guideline development

N-Nitrosodimethylamine was not considered in the WHO *International Standards for Drinking-water* or in the first or second editions of the WHO *Guidelines for Drinking-water Quality*.

Assessment date

The risk assessment was conducted in 2006.

Principal references

WHO (2002) *N-Nitrosodimethylamine*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document No. 38).

WHO (2008) *N-Nitrosodimethylamine in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/HSE/AMR/08.03/8).

12.96 Parathion

Parathion (CAS No. 56-38-2) is a non-systemic insecticide that is used in many countries throughout the world. It is used as a fumigant and acaricide and as a pre-harvest soil and foliage treatment on a wide variety of crops, both outdoors and in greenhouses. Parathion released to the environment will adsorb strongly to the top layer of soil and is not likely to leach significantly. Parathion disappears from surface waters in about a week. The general population is not usually exposed to parathion from air or water. Parathion residues in food are the main source of exposure.

Parathion inhibits cholinesterase activity in all species tested. There has been no evidence of carcinogenicity in 2-year rat studies. JMPR concluded that parathion is not genotoxic.

A health-based value of 10 µg/litre can be calculated for parathion on the basis of an ADI of 0.004 mg/kg of body weight based on a NOAEL of 0.4 mg/kg body weight

per day in a 2-year study in rats for retinal atrophy and inhibition of brain acetylcholinesterase at the higher dose, and using an uncertainty factor of 100. Lower NOAELs in animals, based only on inhibition of erythrocyte or brain acetylcholinesterase, were not considered relevant because of the availability of a NOAEL for erythrocyte acetylcholinesterase inhibition in humans, which was 0.1 mg/kg of body weight per day.

Intake of parathion from all sources is generally low and well below the ADI. As the health-based value is much higher than parathion concentrations likely to be found in drinking-water, the presence of parathion in drinking-water under usual conditions is unlikely to represent a hazard to human health. For this reason, the establishment of a guideline value for parathion is not deemed necessary.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to parathion, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Parathion was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (1996) *Pesticide residues in food – 1995 evaluations. Part II – Toxicological and environmental*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/96.48).

WHO (2003) *Parathion in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/110).

12.97 Pendimethalin

Pendimethalin (CAS No. 40487-42-1) is a pre-emergence herbicide that is fairly immobile and persistent in soil. It is used in large amounts in Japan (5000 tonnes per year). It is lost through photodegradation, biodegradation and volatilization. The leaching potential of pendimethalin appears to be very low, but little is known about its more polar degradation products.

12. CHEMICAL FACT SHEETS

Guideline value	0.02 mg/litre
Occurrence	Rarely been found in drinking-water in the limited studies available (detection limit 0.01 µg/litre)
TDI	5 µg/kg of body weight, based on evidence of slight liver toxicity even at the lowest dose tested (5 mg/kg of body weight) in a long-term rat feeding study, with an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for a combination of the use of a LOAEL instead of a NOAEL and limitations of the database)
Limit of detection	0.01 µg/litre by GC/MS
Treatment achievability	1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

In a short-term dietary study in rats, a variety of indications of hepatotoxicity as well as increased kidney weights in males were observed at the highest dose level. In a long-term dietary study, some toxic effects (hyperglycaemia in the mouse and hepatotoxicity in the rat) were present even at the lowest dose level. On the basis of available data, pendimethalin does not appear to have significant mutagenic activity. Long-term studies in mice and rats have not provided evidence of carcinogenicity; however, these studies have some important methodological limitations.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to pendimethalin, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Pendimethalin was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines established a health-based guideline value of 0.02 mg/litre for pendimethalin in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Pendimethalin in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/41).

12.98 Pentachlorophenol (PCP)

PCP (CAS No. 87-86-5) and other chlorophenols are used primarily for protecting wood from fungal growth. Food is usually the major source of exposure to PCP unless there is a specific local chlorophenol contamination of drinking-water or exposure from log homes treated with PCP.

Provisional guideline value	0.009 mg/litre The guideline value is considered provisional because of the variations in metabolism between experimental animals and humans.
Occurrence	Concentrations in water samples are usually below 10 µg/litre, although much higher concentrations in groundwater may be measured under certain conditions.
Basis of guideline derivation	Multistage modelling of tumour incidence in a US NTP bioassay without incorporation of a body surface area correction, recognizing that there are interspecies differences in metabolism between animals and humans, with an important metabolite formed in rats being only a minor metabolite in humans
Limit of detection	0.005–0.01 µg/litre by GC with ECD
Treatment achievability	0.4 µg/litre should be achievable using GAC
Additional comments	The concentration of PCP associated with a 10 ⁻⁵ upper-bound excess lifetime cancer risk is similar to the guideline value established in the second edition, so that guideline value is retained.

Toxicological review

IARC classified PCP in Group 2B (the agent is possibly carcinogenic to humans) on the basis of inadequate evidence of carcinogenicity in humans but sufficient evidence in experimental animals. There is suggestive, although inconclusive, evidence of the carcinogenicity of PCP from epidemiological studies of populations exposed to mixtures that include PCP. Conclusive evidence of carcinogenicity has been obtained in one animal species (mice). Although there are notable variations in metabolism between experimental animals and humans, it was considered prudent to treat PCP as a potential carcinogen.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to PCP, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a health-based guideline value of 0.01 mg/litre was recommended for PCP. The 1993 *Guidelines* established a health-based guideline value of 0.009 mg/litre for PCP in drinking-water. This value was considered provisional because PCP was evaluated only at the Final Task Group Meeting on the basis of an EHC monograph (No. 71). The concentration of PCP associated

with a 10^{-5} upper-bound excess lifetime cancer risk was found to be similar to the provisional guideline value established in 1993, and so that provisional guideline value was retained in the addendum to the Guidelines, published in 1998.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Pentachlorophenol in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/62).

12.99 Permethrin

Permethrin (CAS No. 52645-53-1) is a contact insecticide effective against a broad range of pests in agriculture, forestry and public health. It has been used as a larvicide to control aquatic invertebrates in water mains. Permethrin is photodegraded both in water and on soil surfaces. In soil, permethrin is rapidly degraded by hydrolysis and microbial action under aerobic conditions. Exposure of the general population to permethrin is mainly via the diet.

Guideline value	0.3 mg/litre (when permethrin is used as a larvicide) This guideline value is applicable where permethrin is applied directly to water as a larvicide. In other situations, it is not considered necessary to derive a health-based guideline value (see Additional comments below).
Occurrence	Concentrations as high as 0.8 mg/litre have been recorded in surface water; in the United Kingdom, levels in drinking-water are below 0.1 µg/litre, but no data were located from elsewhere.
ADI	0.05 mg/kg of body weight, established for technical-grade permethrin with <i>cis</i> : <i>trans</i> ratios of 25:75 to 40:60 on the basis of a NOAEL of 100 mg/kg, equivalent to 5 mg/kg of body weight per day, in a 2-year study in rats, which was based on clinical signs and changes in body and organ weights and blood chemistry at 500 mg/kg, and a NOAEL of 5 mg/kg of body weight per day in a 1-year study in dogs, based on reduced body weight at 100 mg/kg of body weight per day, and applying an uncertainty factor of 100
Limit of detection	0.05 µg/litre by gas-liquid chromatography with an ECD or FID
Treatment achievability	Permethrin adsorbs to a wide range of materials and is readily removed by conventional treatment methods; neither <i>cis</i> - nor <i>trans</i> -permethrin reacts with chlorine under normal disinfection conditions.

Guideline derivation	
● allocation to water	20% (where permethrin is used as a larvicide in water)
● weight	60 kg
● consumption	2 litres/day
Additional comments	<ul style="list-style-type: none"> ● A health-based value of 20 µg/litre (rounded value) can be derived by allocating 1% of the ADI to drinking-water, because there is significant exposure to permethrin from food. However, because permethrin usually occurs in drinking-water at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a health-based guideline value where permethrin is not added directly to water as a larvicide. ● Adding permethrin directly to drinking-water for public health purposes is not recommended by WHO, as part of its policy to exclude the use of any pyrethroids for larviciding of mosquito vectors of human disease. This policy is based on concern over the possible accelerated development of vector resistance to synthetic pyrethroids, which, in their application to insecticide-treated mosquito nets, are crucial in the current global anti-malaria strategy.

Toxicological review

Technical-grade permethrin is of low acute toxicity. The *cis* isomer is considerably more toxic than the *trans* isomer. IARC has classified permethrin in Group 3 (not classifiable as to its carcinogenicity to humans), as there are no human data and only limited data from animal studies. Permethrin is not genotoxic. JMPR has concluded that technical-grade permethrin is not a reproductive or developmental toxin.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to permethrin, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Permethrin was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the second edition of the *Guidelines* (1993) established a health-based guideline value of 0.02 mg/litre for permethrin in drinking-water, based on an ADI established by JMPR in 1987 for 2:3 and 1:3 *cis:trans*-permethrin and recognizing the significant exposure to permethrin from the environment. It was noted that if permethrin is to be used as a larvicide for the control of mosquitoes and other insects of health significance in drinking-water sources, the share of the ADI allocated to drinking-water may be increased.

Assessment date

The risk assessment was conducted in 2004.

Principal references

FAO/WHO (2000) *Pesticide residues in food – 1999. Evaluations – 1999. Part II – Toxicology*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/00.4).

WHO (2005) *Permethrin in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/111).

12.99(a) Petroleum products

Petroleum products are used in large quantities, primarily as fuels. They are complex mixtures of chemicals derived from crude oil by distillation and fractionation. They consist primarily of a wide range of aliphatic and aromatic hydrocarbons, many of which are of extremely low solubility in water. Petroleum products are widely stored and handled and are often spilt. The primary concern for drinking-water is the potential for spills into source water, penetration of distribution systems and contamination of drinking-water treatment works.

Exposure to the constituents of petroleum products through drinking-water is frequently short term, as the result of an accidental spill or short-term incident. Such incidents may lead to high concentrations of total petroleum hydrocarbons (TPH). However, a number of the most soluble aromatic hydrocarbons will be detectable by taste and/or odour at concentrations below those concentrations of concern for health, particularly for short-term exposure. Substances such as the alkyl benzenes and the alkyl naphthalenes have taste and odour thresholds of a few micrograms per litre. In view of the above, it is not considered appropriate to set a formal health-based guideline value for petroleum products in drinking-water.

In the event of a spill, it may be necessary to carry out a context-specific assessment of the risk to health. The fact that petroleum products are complex mixtures of many individual hydrocarbons is a complicating factor in determining the potential risks to consumers. The traditional approach of evaluating individual chemicals in assessing the risks from drinking-water is, therefore, largely inappropriate. In order to overcome this difficulty, it is more practical to consider a series of hydrocarbon fractions and to determine appropriate tolerable concentrations for those fractions. The most widely accepted approach is that developed by the Total Petroleum Hydrocarbons Criteria Working Group in the USA, which divided TPH into a series of aliphatic and aromatic fractions based on the number of carbon atoms and the boiling point, to give equivalent carbon numbers.

This pragmatic approach provides a suitable basis for assessing the potential health risks associated with larger-scale contamination of drinking-water by petroleum products. The allocation of 10% of each of the reference doses, equivalent to TDIs, for the various fractions to drinking-water provides a conservative assessment of the risks. Although the approach is based on the analysis of hydrocarbon fractions, most

are of low solubility, and the most soluble fractions, consisting largely of lower molecular weight aromatic hydrocarbons, will be present in the greatest concentration.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first, second and third editions of the *Guidelines for Drinking-water Quality* did not refer to petroleum products in general, although guideline values have been established for individual petroleum hydrocarbons (e.g., benzene, ethylbenzene, toluene, xylenes) and individual polycyclic aromatic hydrocarbon contaminants of petroleum products (e.g., benzo(a)pyrene).

Assessment date

The risk assessment was conducted in 2004.

Principal reference

WHO (2005) *Petroleum products in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/123).

12.100 pH

No health-based guideline value is proposed for pH. Although pH usually has no direct impact on consumers, it is one of the most important operational water quality parameters (see chapter 10).

History of guideline development

The 1958 WHO *International Standards for Drinking-water* suggested that pH less than 6.5 or greater than 9.2 would markedly impair the potability of the water. The 1963 and 1971 International Standards retained the pH range 6.5–9.2 as the allowable or permissible range. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value pH range of 6.5–8.5 was established for pH, based on aesthetic considerations. It was noted that the acceptable range of pH may be broader in the absence of a distribution system. No health-based guideline value was proposed for pH in the 1993 Guidelines. Although pH usually has no direct impact on consumers, it is one of the most important operational water quality parameters, the optimum pH required often being in the range 6.5–9.5.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2007) *pH in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/07.01/1).

12.101 2-Phenylphenol and its sodium salt

2-Phenylphenol (CAS No. 90-43-7) is used as a disinfectant, bactericide and virucide. In agriculture, it is used in disinfecting fruits, vegetables and eggs. It is also used as a general surface disinfectant in hospitals, nursing homes, veterinary hospitals, poultry farms, dairy farms, commercial laundries, barbershops and food processing plants. 2-Phenylphenol is readily degraded in surface waters, with a half-life of about 1 week in river water.

2-Phenylphenol has been determined to be of low toxicity. Both 2-phenylphenol and its sodium salt are carcinogenic in male rats, and 2-phenylphenol is carcinogenic in male mice. However, urinary bladder tumours observed in male rats and liver tumours observed in male mice exposed to 2-phenylphenol appear to be threshold phenomena that are species- and sex-specific. JMPR has concluded that 2-phenylphenol is unlikely to represent a carcinogenic risk to humans. Although a working group convened by IARC has classified 2-phenylphenol, sodium salt, in Group 2B (possibly carcinogenic to humans) and 2-phenylphenol in Group 3 (not classifiable as to its carcinogenicity to humans), JMPR noted that the IARC classification is based on hazard identification, not risk assessment, and is furthermore limited to published literature, excluding unpublished studies on toxicity and carcinogenicity. JMPR also concluded that there are unresolved questions about the genotoxic potential of 2-phenylphenol.

A health-based value of 1 mg/litre can be calculated for 2-phenylphenol on the basis of an ADI of 0.4 mg/kg of body weight, based on a NOAEL of 39 mg/kg of body weight per day in a 2-year toxicity study for decreased body weight gain and hyperplasia of the urinary bladder and carcinogenicity of the urinary bladder in male rats, using an uncertainty factor of 100. Because of its low toxicity, however, the health-based value derived for 2-phenylphenol is much higher than 2-phenylphenol concentrations likely to be found in drinking-water. Under usual conditions, therefore, the presence of 2-phenylphenol in drinking-water is unlikely to represent a hazard to human health. For this reason, the establishment of a guideline value for 2-phenylphenol is not deemed necessary.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to 2-phenylphenol, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. 2-Phenylphenol was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*,

published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998.

Assessment date

The risk assessment was conducted in 2003.

Principal references

FAO/WHO (2000) *Pesticide residues in food – 1999 evaluations. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/00.4).

WHO (2003) *2-Phenylphenol and its sodium salt in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/69).

12.102 Polynuclear aromatic hydrocarbons (PAHs)

PAHs form a class of diverse organic compounds each containing two or more fused aromatic rings of carbon and hydrogen atoms. Most PAHs enter the environment via the atmosphere from a variety of combustion processes and pyrolysis sources. Owing to their low solubility and high affinity for particulate matter, they are not usually found in water in notable concentrations. The main source of PAH contamination in drinking-water is usually the coal-tar coating of drinking-water distribution pipes, used to protect the pipes from corrosion. Fluoranthene is the most commonly detected PAH in drinking-water and is associated primarily with coal-tar linings of cast iron or ductile iron distribution pipes. PAHs have been detected in a variety of foods as a result of the deposition of airborne PAHs and in fish from contaminated waters. PAHs are also formed during some methods of food preparation, such as charbroiling, grilling, roasting, frying or baking. For the general population, the major routes of exposure to PAHs are from food and ambient and indoor air. The use of open fires for heating and cooking, which is common especially in developing countries, may increase PAH exposure. Where there are elevated levels of contamination by coal-tar coatings of water pipes, PAH intake from drinking-water could equal or even exceed that from food.

Guideline value for benzo[a]pyrene (BaP)	0.0007 mg/litre (0.7 µg/litre)
Occurrence	PAH levels in uncontaminated groundwater usually in range 0–5 ng/litre; concentrations in contaminated groundwater may exceed 10 µg/litre; typical concentration range for sum of selected PAHs in drinking-water is from about 1 ng/litre to 11 µg/litre

Basis of guideline derivation	Based on an oral carcinogenicity study in mice and calculated using a two-stage birth–death mutation model, which incorporates variable dosing patterns and time of killing; quantification of dose–response for tumours, on the basis of new studies in which the carcinogenicity of BaP was examined following oral administration in mice, but for which the number of dose groups was smaller, confirms this value
Limit of detection	0.01 µg/litre by GC/MS and reverse-phase HPLC with a fluorescence detector
Treatment achievability	0.05 µg/litre should be achievable using coagulation
Additional comments	<ul style="list-style-type: none"> • The presence of significant concentrations of BaP in drinking-water in the absence of very high concentrations of fluoranthene indicates the presence of coal-tar particles, which may arise from seriously deteriorating coal-tar pipe linings. • It is recommended that the use of coal-tar-based and similar materials for pipe linings and coatings on storage tanks be discontinued.

Toxicological review

Evidence that mixtures of PAHs are carcinogenic to humans comes primarily from occupational studies of workers following inhalation and dermal exposure. No data are available for humans for the oral route of exposure. There are few data on the oral toxicity of PAHs other than BaP, particularly in drinking-water. Relative potencies of carcinogenic PAHs have been determined by comparison of data from dermal and other studies. The order of potencies is consistent, and this scheme therefore provides a useful indicator of PAH potency relative to BaP.

A health-based value of 4 µg/litre can be calculated for fluoranthene on the basis of a NOAEL of 125 mg/kg of body weight per day for increased serum glutamate–pyruvate transaminase levels, kidney and liver pathology, and clinical and haematological changes in a 13-week oral gavage study in mice, using an uncertainty factor of 10000 (100 for inter- and intraspecies variation, 10 for the use of a sub-chronic study and inadequate database and 10 because of clear evidence of co-carcinogenicity with BaP in mouse skin painting studies). However, this health-based value is significantly above the concentrations normally found in drinking-water. Under usual conditions, therefore, the presence of fluoranthene in drinking-water does not represent a hazard to human health. For this reason, the establishment of a guideline value for fluoranthene is not deemed necessary.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to PAHs. The 1971 *International Standards* stated that some PAHs are known to be carcinogenic and that the concentrations of six representative PAH compounds (fluoranthene, 3,4-benzfluoranthene, 11,12-benzfluoranthene, 3,4-benzpyrene, 1,12-benzpyrene and indeno [1,2,3-cd] pyrene) should therefore not, in general, exceed 0.0002 mg/litre. In the first edition of the *Guidelines for Drinking-water Quality*,

published in 1984, the only PAH for which there was sufficient substantiated toxicological evidence to set a guideline value was BaP. A health-based guideline value of 0.00001 mg/litre was recommended for BaP, while noting that the mathematical model appropriate to chemical carcinogens that was used in its derivation involved considerable uncertainty. It was also recommended that the control of PAHs in drinking-water should be based on the concept that the levels found in unpolluted groundwater should not be exceeded. The 1993 Guidelines concluded that there were insufficient data available to derive drinking-water guidelines for PAHs other than BaP. The guideline value for BaP, corresponding to an upper-bound excess lifetime cancer risk of 10^{-5} , was calculated to be 0.0007 mg/litre. This guideline value was retained in the addendum to the second edition of the Guidelines, published in 1998, as it was confirmed by new studies on the carcinogenicity of the compound. It was also recommended that the use of coal-tar-based and similar materials for pipe linings and coatings on storage tanks be discontinued. Although a health-based value for fluoranthene was calculated in the addendum, it was significantly above the concentrations found in drinking-water, and it was concluded that, under usual conditions, the presence of fluoranthene in drinking-water does not represent a hazard to human health; thus, the establishment of a guideline value for fluoranthene was not deemed necessary. As there are few data on the oral toxicity of other PAHs, particularly in drinking-water, relative potencies of carcinogenic PAHs were determined by comparison of data from dermal and other studies, which provides a useful indicator of PAH potency relative to BaP.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Polynuclear aromatic hydrocarbons in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/59).

12.103 Propanil

Propanil (CAS No. 709-98-8) is a contact post-emergence herbicide used to control broad-leaved and grassy weeds, mainly in rice. It is a mobile compound with affinity for the water compartment. Propanil is not, however, persistent, being easily transformed under natural conditions to several metabolites. Two of these metabolites, 3,4-dichloroaniline and 3,3',4,4'-tetrachloroazobenzene, are more toxic and more persistent than the parent compound. Although used in a number of countries, propanil has only occasionally been detected in groundwater.

Although a health-based value for propanil can be derived, this has not been done, because propanil is readily transformed into metabolites that are more toxic. Therefore, a guideline value for the parent compound is considered inappropriate, and there are inadequate data on the metabolites to allow the derivation of a guideline value for them. Authorities should consider the possible presence in water of more toxic environmental metabolites.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to propanil, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Propanil was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 *Guidelines* established a health-based guideline value of 0.02 mg/litre for propanil in drinking-water, noting that in applying this guideline, authorities should consider the possible presence of more toxic metabolites in water.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Propanil in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/112).

12.104 Pyriproxyfen

Pyriproxyfen (CAS No. 95737-68-1) is a broad-spectrum insect growth regulator with insecticidal activity against public health insect pests: houseflies, mosquitoes and cockroaches. In agriculture and horticulture, pyriproxyfen has registered uses for the control of scale, whitefly, bollworm, jassids, aphids and cutworms. Pyriproxyfen is used on citrus fruit in Israel, South Africa, Spain and Italy. Pyriproxyfen is one of several insecticides used for the control of the red imported fire ant (*Solenopsis invicta*) in California, USA. Pyriproxyfen has also been considered by WHO for vector control under its Pesticides Evaluation Scheme.

Pyriproxyfen degrades rapidly in soil under aerobic conditions, with a half-life of 6.4–36 days. Pyriproxyfen disappeared from aerobic lake water–sediment systems with half-lives ranging from 16 to 21 days. As pyriproxyfen is a relatively new pesticide, few environmental data have been collected. Intake of pyriproxyfen from all sources is generally low and below the ADI.

Guideline value	0.3 mg/litre This guideline value is not intended for pyriproxyfen used as a vector control agent in drinking-water (see section 12.126.5).
Occurrence	No detectable concentrations found in surface water in the USA
ADI	0–0.1 mg/kg of body weight based on an overall NOAEL of 10 mg/kg of body weight per day for increased relative liver weight and increased total plasma cholesterol concentration in male dogs in two 1-year toxicity studies, using an uncertainty factor of 100
Limit of detection	0.1 µg/litre by organic solvent extraction followed by HPLC/UV detection; 0.02 mg/kg by gas–liquid chromatography with NPD
Treatment achievability	No data available; 1 µg/litre should be achievable using GAC
Guideline derivation	
• allocation to water	10% of ADI (to account for exposure through food)
• weight	60-kg adult
• consumption	2 litres/day

Toxicological review

JMPR concluded that pyriproxyfen was not carcinogenic or genotoxic. In short- and long-term studies of the effects of pyriproxyfen in mice, rats and dogs, the liver (increases in liver weight and changes in plasma lipid concentrations, particularly cholesterol) was the main toxicological target. Young animals do not appear to be significantly more sensitive than adults.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to pyriproxyfen, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Pyriproxyfen was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998. In the third edition of the Guidelines, a guideline value of 0.3 mg/litre was established for pyriproxyfen in drinking-water.

Assessment date

The risk assessment was conducted in 2004. The background document was revised in 2008 based on FAO/WHO (2000).

Principal references

- FAO/WHO (2000) *Pesticide residues in food – 1999 evaluations. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/00.4).
- WHO (2008) *Pyriproxyfen in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/HSE/AMR/08.03/10).

12.105 Selenium

Selenium is present in the Earth's crust, often in association with sulfur-containing minerals. Selenium is an essential trace element, and foodstuffs such as cereals, meat

and fish are the principal source of selenium in the general population. Levels in food also vary greatly according to geographical area of production.

Guideline value	0.01 mg/litre
Occurrence	Levels in drinking-water vary greatly in different geographical areas but are usually much less than 0.01 mg/litre.
NOAEL in humans	Estimated to be about 4 µg/kg of body weight per day, based on data in which a group of 142 persons with a mean daily intake of 4 µg/kg body weight showed no clinical or biochemical signs of selenium toxicity
Limit of detection	0.5 µg/litre by AAS with hydride generation
Treatment achievability	0.01 mg/litre should be achievable using coagulation for selenium(IV) removal; selenium(VI) is not removed by conventional treatment processes
Guideline derivation	
● allocation to wate	10% of NOAEL
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

Selenium is an essential element for humans, with a recommended daily intake of about 1 µg/kg of body weight for adults. Selenium compounds have been shown to be genotoxic in *in vitro* systems with metabolic activation, but not in humans. There was no evidence of teratogenic effects in monkeys. Long-term toxicity in rats is characterized by depression of growth and liver pathology. In humans, the toxic effects of long-term selenium exposure are manifested in nails, hair and liver. Data from China indicate that clinical and biochemical signs occur at a daily intake above 0.8 mg. Daily intakes of Venezuelan children with clinical signs were estimated to be about 0.7 mg on the basis of their blood levels and the Chinese data on the relationship between blood level and intake. Effects on synthesis of a liver protein were also seen in a small group of patients with rheumatoid arthritis given selenium at a rate of 0.25 mg/day in addition to selenium from food. No clinical or biochemical signs of selenium toxicity were reported in a group of 142 persons with a mean daily intake of 0.24 mg (maximum 0.72 mg) from food.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* recommended a maximum allowable concentration of 0.05 mg/litre for selenium, based on health concerns. In the 1963 *International Standards*, this value was lowered to 0.01 mg/litre, which was retained in the 1971 *International Standards* as a tentative upper concentration limit, while recognizing that selenium is an essential trace element for some species. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, the guideline value of 0.01 mg/litre was again retained, although it was noted that in areas of

relatively higher or lower selenium dietary intake, the guideline value may have to be modified accordingly. The 1993 Guidelines proposed a health-based guideline value of 0.01 mg/litre on the basis of human studies.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Selenium in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/13).

12.106 Silver

Silver occurs naturally mainly in the form of its very insoluble and immobile oxides, sulfides and some salts. It has occasionally been found in groundwater, surface water and drinking-water at concentrations above 5 µg/litre. Levels in drinking-water treated with silver for disinfection may be above 50 µg/litre. Recent estimates of daily intake are about 7 µg per person.

Only a small percentage of silver is absorbed. Retention rates in humans and laboratory animals range between 0 and 10%.

The only obvious sign of silver overload is argyria, a condition in which skin and hair are heavily discoloured by silver in the tissues. An oral NOAEL for argyria in humans for a total lifetime intake of 10 g of silver was estimated on the basis of human case reports and long-term animal experiments.

The low levels of silver in drinking-water, generally below 5 µg/litre, are not relevant to human health with respect to argyria. On the other hand, special situations exist where silver salts may be used to maintain the bacteriological quality of drinking-water. Higher levels of silver, up to 0.1 mg/litre (this concentration gives a total dose over 70 years of half the human NOAEL of 10 g), could be tolerated in such cases without risk to health.

There are no adequate data with which to derive a health-based guideline value for silver in drinking-water.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to silver. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was not considered necessary to establish a guideline value for silver in drinking-water. No health-based guideline value for silver was proposed in the 1993 Guidelines. Where silver salts are used to maintain the bacteriological quality of

drinking-water, levels of silver up to 0.1 mg/litre can be tolerated without risk to health.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Silver in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/14).

12.107 Simazine

Simazine (CAS No. 122-34-9) is a pre-emergence herbicide used on a number of crops as well as in non-crop areas. It is fairly resistant to physical and chemical dissipation processes in the soil. It is persistent and mobile in the environment.

Guideline value	0.002 mg/litre
Occurrence	Frequently detected in groundwater and surface water at concentrations of up to a few micrograms per litre
TDI	0.52 µg/kg of body weight, based on a NOAEL of 0.52 mg/kg of body weight from a long-term study in the rat (based on weight changes, effects on haematological parameters and an increase in mammary tumours) and an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for possible non-genotoxic carcinogenicity)
Limit of detection	0.01 µg/litre by GC/MS; 0.1–0.2 µg/litre by GC with flame thermionic detection
Treatment achievability	0.1 µg/litre should be achievable using GAC
Guideline derivation	
• allocation to water	10% of TDI
• weight	60-kg adult
• consumption	2 litres/day

Toxicological review

Simazine does not appear to be genotoxic in mammalian systems. Recent studies have shown an increase in mammary tumours in the female rat but no effects in the mouse. IARC has classified simazine in Group 3.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to simazine, but the 1971 International Standards suggested that pesticide residues that

may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Simazine was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 Guidelines established a health-based guideline value of 0.002 mg/litre for simazine in drinking-water.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Simazine in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/42).

12.108 Sodium

Sodium salts (e.g., sodium chloride) are found in virtually all food (the main source of daily exposure) and drinking-water. Although concentrations of sodium in potable water are typically less than 20 mg/litre, they can greatly exceed this in some countries. The levels of sodium salts in air are normally low in relation to those in food or water. It should be noted that some water softeners can add significantly to the sodium content of drinking-water.

No firm conclusions can be drawn concerning the possible association between sodium in drinking-water and the occurrence of hypertension. Therefore, no health-based guideline value is proposed. However, concentrations in excess of 200 mg/litre may give rise to unacceptable taste (see chapter 10).

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to sodium. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was concluded that there was insufficient evidence to justify a guideline value for sodium in water based on health risk considerations, but it was noted that intake of sodium from drinking-water may be of greater significance in persons who require a sodium-restricted diet and bottle-fed infants. A guideline value of 200 mg/litre was established for sodium based on taste considerations. No health-based guideline value was proposed for sodium in the 1993 Guidelines, as no firm conclusions could be drawn concerning the possible association between sodium in drinking-water and the occurrence of hypertension. However, concentrations in excess of 200 mg/litre may give rise to unacceptable taste.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Sodium in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/15).

12.108(a) Sodium dichloroisocyanurate

Sodium dichloroisocyanurate is the sodium salt of a chlorinated hydroxytriazine and is used as a source of free available chlorine, in the form of hypochlorous acid, for the disinfection of water. It is widely used as a stable source of chlorine for the disinfection of swimming pools and in the food industry. It is also used as a means of disinfecting drinking-water, primarily in emergencies, when it provides an easy-to-use source of free chlorine, and, more recently, as the form of chlorine for household point-of-use water treatment.

Guideline values	50 mg/litre (as sodium dichloroisocyanurate) 40 mg/litre (as cyanuric acid)
Occurrence	Where sodium dichloroisocyanurate is used for the disinfection of drinking-water, exposure will be to both the chlorinated species and residual cyanuric acid. The concentrations will relate directly to the quantities added to achieve adequate disinfection.
TDI	2.2 mg/kg of body weight for anhydrous sodium dichloroisocyanurate and 1.54 mg/kg of body weight for cyanuric acid, based on a NOEL of 154 mg/kg of body weight per day (equivalent to 220 mg/kg of body weight per day as anhydrous sodium dichloroisocyanurate) for urinary tract and cardiac lesions from a 2-year study on exposure of rats to sodium cyanurate and using an uncertainty factor of 100
Limit of detection	0.001 mg/litre by GC with flame thermionic specific detection; 0.05 mg/litre by reverse-phase LC with UV detection; 0.09 mg/litre by GC with MS selective ion monitoring
Treatment achievability	At very high chlorine doses (up to 10 mg/litre), the sodium cyanurate concentration would be below 11 mg/litre. In emergency situations, "topping up" might be done in an attempt to maintain a free chlorine residual, but this practice should be discouraged. In this case, it would be possible for the sodium cyanurate concentration to build up to undesirable levels. In such cases, it would be very desirable to monitor the concentration of sodium cyanurate.
Guideline derivation	
● allocation to water	80% of TDI
● weight	60-kg adult
● consumption	2 litres/day

- Additional considerations
- The controlling factors are the level of free chlorine and the residue of cyanuric acid, particularly if there is topping up of chlorine in a static system under emergency conditions. The concentration of free chlorine should normally be such that it should not give rise to unacceptable tastes and should not normally exceed the guideline value of 5 mg/litre for free chlorine.
 - Sodium dichloroisocyanurate used for disinfecting drinking-water should be of adequate purity so that there is no increase in any inorganic or organic contaminants in the drinking-water. The amounts of sodium dichloroisocyanurate used should be the lowest consistent with adequate disinfection, and the concentrations of cyanuric acid should be managed to be kept as low as is reasonably possible.
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Toxicological review

Studies of the toxicity of sodium cyanurate are appropriate for assessing the safety of sodium dichloroisocyanurate, because any residues of intact sodium dichloroisocyanurate in drinking-water would be rapidly converted to cyanuric acid on contact with saliva. Both sodium dichloroisocyanurate and sodium cyanurate have low acute oral toxicity. Sodium cyanurate does not induce any genotoxic, carcinogenic or teratogenic effects. The NOEL from which the guideline value was derived was based on multiple lesions of the urinary tract (calculi and hyperplasia, bleeding and inflammation of the bladder epithelium, dilated and inflamed ureters and renal tubular nephrosis) and cardiac lesions (acute myocarditis, necrosis and vascular mineralization) in male rats exposed at the next higher dose.

History of guideline development

Sodium dichloroisocyanurate was not considered in the WHO *International Standards for Drinking-water* or in the first or second editions of the WHO *Guidelines for Drinking-water Quality*.

Assessment date

The risk assessment was conducted in 2007.

Principal references

WHO (2004) *Evaluation of certain food additives and contaminants*. Sixty-first report of the Joint FAO/WHO Committee on Food Additives. Geneva, World Health Organization (WHO Technical Report Series No. 922; http://whqlibdoc.who.int/trs/WHO_TRS_922.pdf).

WHO (2008) *Sodium dichloroisocyanurate in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/HSE/AMR/08.03/3).

12.109 Styrene

Styrene, which is used primarily for the production of plastics and resins, is found in trace amounts in surface water, drinking-water and food. In industrial areas, exposure via air can result in intake of a few hundred micrograms per day. Smoking may increase daily exposure by up to 10-fold.

Guideline value	0.02 mg/litre
Occurrence	Has been detected in drinking-water and surface water at concentrations below 1 µg/litre
TDI	7.7 µg/kg of body weight, based on a NOAEL of 7.7 mg/kg of body weight per day for decreased body weight observed in a 2- year drinking-water study in rats, and using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the carcinogenicity and genotoxicity of the reactive intermediate styrene-7,8-oxide)
Limit of detection	0.3 µg/litre by GC with photoionization detection and confirmation by MS
Treatment achievability	0.02 mg/litre may be achievable using GAC
Guideline derivation	
• allocation to water	10% of TDI
• weight	60-kg adult
• consumption	2 litres/day
Additional comments	Styrene may affect the acceptability of drinking-water at the guideline value.

Toxicological review

Following oral or inhalation exposure, styrene is rapidly absorbed and widely distributed in the body, with a preference for lipid depots. It is metabolized to the active intermediate styrene-7,8-oxide, which is conjugated with glutathione or further metabolized. Metabolites are rapidly and almost completely excreted in urine. Styrene has a low acute toxicity. In short-term toxicity studies in rats, impairment of glutathione transferase activity and reduced glutathione concentrations were observed. In *in vitro* tests, styrene has been shown to be mutagenic in the presence of metabolic

activation only. In *in vitro* as well as in *in vivo* studies, chromosomal aberrations have been observed, mostly at high doses of styrene. The reactive intermediate styrene-7,8-oxide is a direct-acting mutagen. In long-term studies, orally administered styrene increased the incidence of lung tumours in mice at high dose levels but had no carcinogenic effect in rats. Styrene-7,8-oxide was carcinogenic in rats after oral administration. IARC has classified styrene in Group 2B. The available data suggest that the carcinogenicity of styrene is due to overloading of the detoxification mechanism for styrene-7,8-oxide (e.g., glutathione depletion).

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to styrene. The 1993 Guidelines established a health-based guideline value of 0.02 mg/litre for styrene, noting that styrene may affect the acceptability of drinking-water at this concentration.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Styrene in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/27).

12.110 Sulfate

Sulfates occur naturally in numerous minerals and are used commercially, principally in the chemical industry. They are discharged into water in industrial wastes and through atmospheric deposition; however, the highest levels usually occur in ground-water and are from natural sources. In general, the average daily intake of sulfate from drinking-water, air and food is approximately 500 mg, food being the major source. However, in areas with drinking-water supplies containing high levels of sulfate, drinking-water may constitute the principal source of intake.

The existing data do not identify a level of sulfate in drinking-water that is likely to cause adverse human health effects. The data from a liquid diet piglet study and from tap water studies with human volunteers indicate a laxative effect at concentrations of 1000–1200 mg/litre but no increase in diarrhoea, dehydration or weight loss.

No health-based guideline is proposed for sulfate. However, because of the gastrointestinal effects resulting from ingestion of drinking-water containing high sulfate levels, it is recommended that health authorities be notified of sources of drinking-water that contain sulfate concentrations in excess of 500 mg/litre. The presence of

sulfate in drinking-water may also cause noticeable taste (see chapter 10) and may contribute to the corrosion of distribution systems.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* suggested that concentrations of sulfate greater than 400 mg/litre would markedly impair the potability of the water. The 1963 and 1971 International Standards retained this value as a maximum allowable or permissible concentration. The first two editions of the International Standards also suggested that concentrations of magnesium plus sodium sulfate in excess of 1000 mg/litre would markedly impair drinking-water potability. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 400 mg/litre for sulfate was established, based on taste considerations. No health-based guideline value for sulfate was proposed in the 1993 Guidelines. However, because of the gastrointestinal effects resulting from ingestion of drinking-water containing high sulfate levels, it was recommended that health authorities be notified of sources of drinking-water that contain sulfate concentrations in excess of 500 mg/litre. The presence of sulfate in drinking-water may also cause noticeable taste at concentrations above 250 mg/litre and may contribute to the corrosion of distribution systems.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Sulfate in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/114).

12.111 2,4,5-T (2,4,5-Trichlorophenoxyacetic acid)

The half-lives for degradation of chlorophenoxy herbicides, including 2,4,5-T (CAS No. 93-76-5), in the environment are in the order of several days. Chlorophenoxy herbicides are not often found in food.

Guideline value	0.009 mg/litre
Occurrence	Chlorophenoxy herbicides not frequently found in drinking-water; when detected, concentrations are usually no greater than a few micrograms per litre
TDI	3 µg/kg of body weight, based on a NOAEL of 3 mg/kg of body weight for reduced body weight gain, increased liver and kidney weights and renal toxicity in a 2-year study in rats, with an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 to take into consideration the suggested association between 2,4,5-T and soft tissue sarcoma and non-Hodgkin lymphoma in epidemiological studies)

Limit of detection	0.02 µg/litre by GC with an ECD
Treatment achievability	1 µg/litre should be achievable using GAC
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

Chlorophenoxy herbicides, as a group, have been classified in Group 2B by IARC. However, the available data from studies in exposed populations and animals do not permit assessment of the carcinogenic potential to humans of any specific chlorophenoxy herbicide. Therefore, drinking-water guidelines for these compounds are based on a threshold approach for other toxic effects. The NOAEL for reproductive effects (reduced neonatal survival, decreased fertility, reduced relative liver weights and thymus weights in litters) of dioxin-free (<0.03 µg/kg) 2,4,5-T in a three-generation reproduction study in rats is the same as the NOAEL for reduced body weight gain, increased liver and kidney weights and renal toxicity in a toxicity study in which rats were fed 2,4,5-T (practically free from dioxin contamination) in the diet for 2 years.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to chlorophenoxy herbicides, including 2,4,5-T, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. 2,4,5-T was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 *Guidelines* established a health-based guideline value of 0.009 mg/litre for 2,4,5-T.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/44).

12.112 Terbutylazine (TBA)

TBA (CAS No. 5915-41-3), a herbicide that belongs to the chlorotriazine family, is used in both pre- and post-emergence treatment of a variety of agricultural crops and

in forestry. Degradation of TBA in natural water depends on the presence of sediments and biological activity.

Guideline value	0.007 mg/litre
Occurrence	Concentrations in water seldom exceed 0.2 µg/litre, although higher concentrations have been observed.
TDI	2.2 µg/kg of body weight, based on a NOAEL of 0.22 mg/kg of body weight for decreased body weight gain at the next higher dose in a 2-year toxicity/carcinogenicity study in rats, with an uncertainty factor of 100 (for inter- and intraspecies variation)
Limit of detection	0.1 µg/litre by HPLC with UV detection
Treatment achievability	0.1 µg/litre should be achievable using GAC
Guideline derivation	
• allocation to water	10% of TDI
• weight	60-kg adult
• consumption	2 litres/day

Toxicological review

There is no evidence that TBA is carcinogenic or mutagenic. In long-term dietary studies in rats, effects on red blood cell parameters in females, an increased incidence of non-neoplastic lesions in the liver, lung, thyroid and testis and a slight decrease in body weight gain were observed.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to TBA, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline value for triazine herbicides, which include TBA, was recommended after a detailed evaluation of the compounds. TBA was not evaluated in the second edition of the *Guidelines for Drinking-water Quality*, published in 1993. In the addendum to the second edition of the Guidelines, published in 1998, a health-based guideline value of 0.007 mg/litre was derived for TBA in drinking-water.

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Terbutylazine in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/63).

12.113 Tetrachloroethene

Tetrachloroethene has been used primarily as a solvent in dry cleaning industries and to a lesser extent as a degreasing solvent. It is widespread in the environment and is found in trace amounts in water, aquatic organisms, air, foodstuffs and human tissue. The highest environmental levels of tetrachloroethene are found in the commercial dry cleaning and metal degreasing industries. Emissions can sometimes lead to high concentrations in groundwater. Tetrachloroethene in anaerobic groundwater may degrade to more toxic compounds, including vinyl chloride.

Guideline value	0.04 mg/litre
Occurrence	Concentrations in drinking-water are generally below 3 µg/litre, although much higher concentrations have been detected in well water (23 mg/litre) and in contaminated groundwater (1 mg/litre).
TDI	14 µg/kg of body weight, based on hepatotoxic effects observed in a 6-week gavage study in male mice and a 90-day drinking-water study in male and female rats, and taking into consideration carcinogenic potential (but not the short length of the study, in view of the database and considerations regarding the application of the dose via drinking-water in one of the two critical studies)
Limit of detection	0.2 µg/litre by GC with ECD; 4.1 µg/litre by GC/MS
Treatment achievability	0.001 mg/litre should be achievable using air stripping
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day

Toxicological review

At high concentrations, tetrachloroethene causes central nervous system depression. Lower concentrations of tetrachloroethene have been reported to damage the liver and the kidneys. IARC has classified tetrachloroethene in Group 2A. Tetrachloroethene has been reported to produce liver tumours in male and female mice, with some evidence of mononuclear cell leukaemia in male and female rats and kidney tumours in male rats. The overall evidence from studies conducted to assess the genotoxicity of tetrachloroethene, including induction of single-strand DNA breaks, mutation in germ cells and chromosomal aberrations *in vitro* and *in vivo*, indicates that tetrachloroethene is not genotoxic.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to tetrachloroethene. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a tentative guideline value of 0.01 mg/litre was recommended; the guideline was designated as tentative because, although the carcinogenicity data did not justify a full guideline value, the compound was considered to have important health implications when present in drinking-water. The 1993 Guidelines established a health-based guideline value of 0.04 mg/litre for tetrachloroethene.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Tetrachloroethene in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/23).

12.114 Toluene

Most toluene (in the form of benzene–toluene–xylene mixtures) is used in the blending of petrol. It is also used as a solvent and as a raw material in chemical production. The main exposure is via air. Exposure is increased by smoking and in traffic.

Guideline value	0.7 mg/litre
Occurrence	Concentrations of a few micrograms per litre have been found in surface water, groundwater and drinking-water; point emissions can lead to higher concentrations in groundwater (up to 1 mg/litre). It may also penetrate plastic pipes from contaminated soil.
TDI	223 µg/kg of body weight, based on a LOAEL of 312 mg/kg of body weight per day for marginal hepatotoxic effects observed in a 13-week gavage study in mice, correcting for 5 days per week dosing and using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the short duration of the study and use of a LOAEL instead of a NOAEL)
Limit of detection	0.13 µg/litre by GC with FID; 6 µg/litre by GC/MS
Treatment achievability	0.001 mg/litre should be achievable using air stripping
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	The guideline value exceeds the lowest reported odour threshold for toluene in water.

Toxicological review

Toluene is absorbed completely from the gastrointestinal tract and rapidly distributed in the body, with a preference for adipose tissue. Toluene is rapidly metabolized and, following conjugation, excreted predominantly in urine. With occupational exposure to toluene by inhalation, impairment of the central nervous system and irritation of mucous membranes are observed. The acute oral toxicity is low. Toluene exerts embryotoxic and fetotoxic effects, but there is no clear evidence of teratogenic activity in laboratory animals and humans. In long-term inhalation studies in rats and mice, there is no evidence for carcinogenicity of toluene. Genotoxicity tests *in vitro* were negative, whereas *in vivo* assays showed conflicting results with respect to chromosomal aberrations. IARC has concluded that there is inadequate evidence for the carcinogenicity of toluene in both experimental animals and humans and classified it as Group 3 (not classifiable as to its carcinogenicity to humans).

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to toluene. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline value was recommended after a detailed evaluation of the compound. The 1993 Guidelines established a health-based guideline value of 0.7 mg/litre for toluene, but noted that this value exceeds the lowest reported odour threshold for toluene in water (0.024 mg/litre).

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Toluene in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/116).

12.115 Total dissolved solids (TDS)

TDS comprise inorganic salts (principally calcium, magnesium, potassium, sodium, bicarbonates, chlorides and sulfates) and small amounts of organic matter that are dissolved in water. TDS in drinking-water originate from natural sources, sewage, urban runoff and industrial wastewater. Salts used for road de-icing in some countries may also contribute to the TDS content of drinking-water. Concentrations of TDS in water vary considerably in different geological regions owing to differences in the solubilities of minerals.

Reliable data on possible health effects associated with the ingestion of TDS in drinking-water are not available, and no health-based guideline value is proposed. However, the presence of high levels of TDS in drinking-water may be objectionable to consumers (see chapter 10).

History of guideline development

The 1958 WHO *International Standards for Drinking-water* suggested that concentrations of total solids greater than 1500 mg/litre would markedly impair the potability of the water. The 1963 and 1971 International Standards retained this value as a maximum allowable or permissible concentration. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 1000 mg/litre was established for TDS, based on taste considerations. No health-based guideline value for TDS was proposed in the 1993 Guidelines, as reliable data on possible health effects associated with the ingestion of TDS in drinking-water were not available. However, the presence of high levels of TDS in drinking-water (greater than 1200 mg/litre) may be objectionable to consumers. Water with extremely low concentrations of TDS may also be unacceptable because of its flat, insipid taste.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Total dissolved solids in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/16).

12.116 Trichloroacetic acid

Chlorinated acetic acids are formed from organic material during water chlorination.

Guideline value	0.2 mg/litre
Occurrence	Detected in US groundwater and surface water distribution systems at mean concentrations of 5.3 µg/litre (range <1.0–80 µg/litre) and 16 µg/litre (range <1.0–174 µg/litre), respectively; maximum concentration (200 µg/litre) measured in chlorinated water in Australia
TDI	32.5 µg/kg of body weight, based on a NOAEL of 32.5 mg/kg of body weight per day from a study in which decreased body weight, increased liver serum enzyme activity and liver histopathology were seen in rats exposed to trichloroacetate in drinking-water for 2 years, incorporating an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for database deficiencies, including the absence of a multigeneration reproductive study, the lack of a developmental study in a second species and the absence of full histopathological data in a second species)
Limit of detection	1 µg/litre by GC with ECD; 1 µg/litre by GC/MS

Treatment achievability	Trichloroacetic acid concentrations in drinking-water are generally below 0.1 mg/litre. Concentrations may be reduced by installing or optimizing coagulation to remove precursors and/or by controlling the pH during chlorination.
Guideline derivation	
● allocation to water	20% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	A similar TDI for trichloroacetate was established by IPCS based on a NOAEL for hepatic toxicity in a long-term study in mice.

Toxicological review

Trichloroacetic acid has been shown to induce tumours in the liver of mice. It has given mixed results in *in vitro* assays for mutations and chromosomal aberrations and has been reported to cause chromosomal aberrations in *in vivo* studies. IARC has classified trichloroacetic acid in Group 3, not classifiable as to its carcinogenicity to humans. The weight of evidence indicates that trichloroacetic acid is not a genotoxic carcinogen.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to trichloroacetic acid. In the 1993 Guidelines, a provisional guideline value of 0.1 mg/litre was derived for trichloroacetic acid, with the provisional designation because of the limitations of the available toxicological database and because there were inadequate data to judge whether the guideline value was technically achievable. It was emphasized that difficulties in meeting the guideline value must never be a reason for compromising adequate disinfection.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Trichloroacetic acid in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/120).

12.117 Trichlorobenzenes (total)

Releases of trichlorobenzenes (TCBs) into the environment occur through their manufacture and use as industrial chemicals, chemical intermediates and solvents. TCBs are found in drinking-water, but rarely at levels above 1 µg/litre. General population exposure will primarily result from air and food.

The TCBs are of moderate acute toxicity. After short-term oral exposure, all three isomers show similar toxic effects, predominantly on the liver. Long-term toxicity and carcinogenicity studies via the oral route have not been carried out, but the data available suggest that all three isomers are non-genotoxic.

A health-based value of 20 µg/litre can be calculated for total TCBs on the basis of a TDI of 7.7 µg/kg of body weight, based on liver toxicity identified in a 13-week rat study, taking into consideration the short duration of the study. However, because TCBs occur at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a health-based guideline value. It should be noted that the health-based value exceeds the lowest reported odour threshold in water.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to TCBs. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was concluded that insufficient health data were available from which to derive a guideline value for 1,2,4-TCB. The 1993 Guidelines proposed a health-based guideline value of 0.02 mg/litre for total TCBs, because of the similarity in the toxicity of the three isomers, but noted that this value exceeds the lowest reported odour threshold in water (0.005 mg/litre for 1,2,4-TCB).

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Trichlorobenzenes in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/117).

12.118 1,1,1-Trichloroethane

1,1,1-Trichloroethane is widely used as a cleaning solvent for electrical equipment, as a solvent for adhesives, coatings and textile dyes and as a coolant and lubricant. It is found mainly in the atmosphere, although it is mobile in soils and readily migrates to groundwaters. 1,1,1-Trichloroethane has been found in only a small proportion of surface waters and groundwaters, usually at concentrations of less than 20 µg/litre; higher concentrations (up to 150 µg/litre) have been observed in a few instances. There appears to be increasing exposure to 1,1,1-trichloroethane from other sources.

1,1,1-Trichloroethane is rapidly absorbed from the lungs and gastrointestinal tract, but only small amounts – about 6% in humans and 3% in experimental animals – are metabolized. Exposure to high concentrations can lead to hepatic steatosis (fatty liver) in both humans and laboratory animals. In a well conducted oral study in mice and rats, effects included reduced liver weight and changes in the kidney consistent

with hyaline droplet neuropathy. IARC has placed 1,1,1-trichloroethane in Group 3. 1,1,1-Trichloroethane does not appear to be mutagenic.

A health-based value of 2 mg/litre can be calculated for 1,1,1-trichloroethane on the basis of a TDI of 0.6 mg/kg of body weight, based on changes in the kidney that were consistent with hyaline droplet nephropathy observed in a 13-week oral study in male rats, and taking into account the short duration of the study. However, because 1,1,1-trichloroethane occurs at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a guideline value.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to 1,1,1-trichloroethane. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline value was recommended after a detailed evaluation of the compound. The 1993 Guidelines proposed a provisional guideline value of 2 mg/litre for 1,1,1-trichloroethane. The value was provisional because it was based on an inhalation study rather than an oral study. It was strongly recommended that an adequate oral toxicity study be conducted to provide more acceptable data for the derivation of a guideline value.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *1,1,1-Trichloroethane in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/65).

12.119 Trichloroethene

Trichloroethene is used primarily in metal degreasing. It is emitted mainly to the atmosphere, but it may also be introduced into groundwater and, to a lesser extent, surface water in industrial effluents. Poor handling as well as improper disposal of trichloroethene in landfills have been the main causes of groundwater contamination. It is expected that exposure to trichloroethene from air will be greater than that from food or drinking-water, unless the drinking-water contains trichloroethene at levels above about 10 µg/litre.

Provisional guideline value	0.02 mg/litre The guideline value is designated as provisional because of deficiencies in the toxicological database.
Occurrence	Due to its high volatility, concentrations are normally low (<1 µg/litre) in surface water; concentrations may be higher (usually below 100 µg/litre) in groundwater systems where volatilization and biodegradation are limited.

12. CHEMICAL FACT SHEETS

TDI	1.46 µg/kg of body weight per day in a developmental toxicity study in rats, based on a BMDL ₁₀ (the lower 95% confidence limit corresponding to a 10% increase in extra risk of fetal heart malformations over background) of 0.146 mg/kg of body weight per day and using an uncertainty factor of 100 for intra- and interspecies variation
Limit of detection	0.01–3.0 µg/litre by purge and trap capillary GC with photoionization detectors or with photoionization detectors and ECD in series; 0.5 µg/litre by purge and trap capillary GC with MS; 0.01 µg/litre by liquid–liquid extraction and GC with ECD; practical quantification limit considered to be achievable by most good laboratories is 5 µg/litre
Treatment achievability	0.002 mg/litre should be achievable by air stripping, possibly in combination with GAC adsorption
Guideline derivation	
● allocation to water	50% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	<ul style="list-style-type: none"> ● The guideline value is protective for both cancer and non-cancer end-points. ● In countries with low rates of ventilation in houses and high rates of showering and bathing, authorities may wish to take the additional exposures through the dermal and inhalation routes into consideration in developing national standards from the provisional guideline value.

Toxicological review

Although trichloroethene appears to be weakly genotoxic in *in vitro* and *in vivo* assays, several of its metabolites are genotoxic, and some are established as known or likely human carcinogens. In view of the sufficient weight of evidence of carcinogenicity in two species of experimental animals with supporting human data, IARC classified trichloroethene as Group 2A (probably carcinogenic to humans). Developmental toxicity is considered to be the critical non-cancer effect, because of the low adverse effect level, the severity of the end-point (heart malformations) and the presence of evidence for similar effects (e.g., cardiac anomalies) from epidemiological studies.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to trichloroethene. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a tentative guideline value of 0.03 mg/litre was recommended; the guideline was designated as tentative because, although carcinogenicity was observed in one species only, the compound occurs relatively frequently in drinking-water. The second edition of the *Guidelines* (1993) established a provisional health-based guideline value of 0.07 mg/litre for trichloroethene. The value was provisional because an uncertainty factor of 3000 was used in its derivation. This guideline value was brought forward to the third edition.

Assessment date

The risk assessment was conducted in 2004.

Principal reference

WHO (2005) *Trichloroethene in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/22).

12.120 Trifluralin

Trifluralin (CAS No. 1582-09-8) is a pre-emergence herbicide used in a number of crops. It has low water solubility and a high affinity for soil. However, biodegradation and photodegradation processes may give rise to polar metabolites that may contaminate drinking-water sources. Although this compound is used in many countries, relatively few data are available concerning contamination of drinking-water.

Guideline value	0.02 mg/litre
Occurrence	Not detected in the small number of drinking-water samples analysed; has been detected in surface water at concentrations above 0.5 µg/litre and rarely in groundwater
TDI	7.5 µg/kg of body weight, based on a NOAEL of 0.75 mg/kg of body weight for mild hepatic effects in a 1-year feeding study in dogs, with an uncertainty factor of 100 (for inter- and intraspecies variation)
Limit of detection	0.05 µg/litre by GC with nitrogen–phosphorus detection
Treatment achievability	1 µg/litre should be achievable using GAC
Guideline derivation	
• allocation to water	10% of TDI
• weight	60-kg adult
• consumption	2 litres/day
Additional comments	Authorities should note that some impure technical grades of trifluralin could contain potent carcinogenic compounds and therefore should not be used.

Toxicological review

Trifluralin of high purity does not possess mutagenic properties. Technical trifluralin of low purity may contain nitroso contaminants and has been found to be mutagenic. No evidence of carcinogenicity was demonstrated in a number of long-term toxicity/carcinogenicity studies with pure (99%) test material. IARC recently evaluated technical-grade trifluralin and assigned it to Group 3.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to trifluralin, but the 1971 *International Standards* suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Trifluralin was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, but the 1993 *Guidelines* established a health-based guideline value of 0.02 mg/litre for trifluralin in drinking-water, noting that authorities should be aware that some impure technical grades of trifluralin could contain potent carcinogenic compounds and therefore should not be used.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Trifluralin in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/43).

12.121 Trihalomethanes (bromoform, bromodichloromethane, dibromochloromethane, chloroform)

Trihalomethanes (THMs) are formed in drinking-water primarily as a result of chlorination of organic matter present naturally in raw water supplies. The rate and degree of THM formation increase as a function of the chlorine and humic acid concentration, temperature, pH and bromide ion concentration. Chloroform is the most common THM and the principal DBP in chlorinated drinking-water. In the presence of bromides, brominated THMs are formed preferentially and chloroform concentrations decrease proportionally. It is assumed that most THMs present in water are ultimately transferred to air as a result of their volatility. For chloroform, for example, individuals may be exposed during showering to elevated concentrations from chlorinated tap water. For the volatile THMs, approximately equal contributions to total exposure come from four areas: ingestion of drinking-water, inhalation of indoor air largely due to volatilization from drinking-water, inhalation and dermal exposure during showering or bathing, and ingestion of food, with all but food exposure arising primarily from drinking-water. Indoor air exposure to the volatile THMs is particularly important in countries with low rates of ventilation in houses and high rates of showering and bathing.

Guideline values

Chloroform	0.3 mg/litre
Bromoform	0.1 mg/litre
Dibromochloromethane (DBCM)	0.1 mg/litre
Bromodichloromethane (BDCM)	0.06 mg/litre

Occurrence	THMs are not expected to be found in raw water (unless near a pollution source) but are usually present in finished or chlorinated water; concentrations are generally below 100 µg/litre. In most circumstances, chloroform is the dominant compound.
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GUIDELINES FOR DRINKING-WATER QUALITY

TDIs

Chloroform	15 µg/kg of body weight, derived from the lower 95% confidence limit for the 5% incidence of hepatic cysts, generated by PBPK modelling, in beagle dogs that ingested chloroform in toothpaste for 7.5 years, using an uncertainty factor of 25 (10 for intraspecies differences in toxicokinetics and toxicodynamics and 2.5 for differences in interspecies toxicodynamics)
Bromoform	17.9 µg/kg of body weight, based on the absence of histopathological lesions in the liver in a well conducted and well documented 90-day study in rats, using an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for possible carcinogenicity and short duration of exposure)
BDCM	21.4 µg/kg of body weight, based on the absence of histopathological effects in the liver in a well conducted and well documented 90-day study in rats, 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
Basis of guideline derivation for BDCM	Application of the linearized multistage model for the observed increases in incidence of kidney tumours in male mice observed in an NTP bioassay, as these tumours yield the most protective value
Limit of detection	0.1–0.2 µg/litre (method detection limits) by purge-and-trap and liquid–liquid extraction and direct aqueous injection in combination with a chromatographic system; 0.1 µg/litre by GC with ECD; 2.2 µg/litre by GC/MS
Treatment achievability	Concentrations of chloroform, bromoform, BDCM and DBCM in drinking-water are generally below 0.05 mg/litre. Concentrations can be reduced by changes to disinfection practice (e.g., reducing organic THM precursors) or using air stripping.

Guideline derivation

- allocation to water 20% of TDI for bromoform and BDCM
75% of TDI for chloroform
- weight 60-kg adult
- consumption 2 litres/day

Additional comments on THMs

For authorities wishing to establish a total THM 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 THMs 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. It is emphasized that adequate disinfection should never be compromised in attempting to meet guidelines for THMs. Nevertheless, in view of the potential link between adverse reproductive outcomes and THMs, particularly brominated THMs, it is recommended that THM levels in drinking-water be kept as low as practicable.

Additional comments on chloroform	<ul style="list-style-type: none"> • In countries with low rates of ventilation in houses and high rates of showering and bathing, the guideline value could be lowered to account for the additional exposures from inhalation of indoor air largely due to volatilization from drinking-water and inhalation and dermal exposure during showering or bathing. • The guideline value is based on the same study as in the third edition; the increase in value is primarily a result of an increase in the allocation of exposure in drinking-water from 50% to 75% to account for the fact that chloroform is used less now than it was in 1993 when the original guideline was developed.
Additional comments on BDCM	<ul style="list-style-type: none"> • Although a health-based value of 21 µg/litre is derived, the previous guideline of 60 µg/litre has been retained for two reasons: 1) both calculations were based on the same study, the only differences being the model and model assumptions used to derive the guideline value; there is therefore no scientific basis on which to justify a change in the guideline value; and 2) BDCM concentrations below 50 µg/litre may be difficult to achieve using currently available technology without compromising the effectiveness of disinfection. • As with chloroform, countries with low rates of ventilation and high rates of showering and bathing may wish to lower the guideline value to account for dermal and inhalation exposures, although, as noted above, concentrations below 50 µg/litre may be difficult to achieve using currently available technology without compromising the effectiveness of disinfection.

Toxicological review

Chloroform

The weight of evidence for genotoxicity of chloroform is considered negative. IARC has classified chloroform as possibly carcinogenic to humans (Group 2B) based on limited evidence of carcinogenicity in humans but sufficient evidence of carcinogenicity in experimental animals. 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. 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.

Bromoform

In an NTP bioassay, 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 (not classifiable as to its carcinogenicity to humans).

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 (not classifiable as to its carcinogenicity to humans).

Bromodichloromethane

IARC has classified BDCM in Group 2B (possibly carcinogenic to humans). BDCM gave both positive and negative results in a variety of *in vitro* and *in vivo* genotoxicity assays. 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. Exposure to BDCM has also been linked to a possible increase in reproductive effects (increased risk for spontaneous abortion or stillbirth).

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to THMs. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline values for THMs other than chloroform were recommended after a detailed evaluation of the compounds. A health-based guideline value of 0.03 mg/litre was established for chloroform only, as few data existed for the remaining THMs and, for most water supplies, chloroform was the most commonly encountered member of the group. It was noted that the guideline value for chloroform was obtained using a linear multistage extrapolation of data obtained from male rats, a mathematical model that involves considerable uncertainty. It was also mentioned that although the available toxicological data were useful in establishing a guideline value for chloroform only, the concentrations of the other THMs should also be minimized. Limits ranging from 0.025 to 0.25 mg/litre, which represent a balance between the levels that can be achieved given certain circumstances and those that are desirable, have been set in several countries for the sum of bromoform, DBCM, BDCM and chloroform. In the second edition of the Guidelines, published in 1993, no guideline value was set for total THMs, but guideline values were established separately for all four THMs. Authorities wishing to establish a total THM standard to account for additive toxicity could use a fractionation approach in which the sum of the ratios of each of the four THMs to their respective guideline values is less than or equal to 1. The 1993 Guidelines established health-based guideline values of 0.1 mg/litre for both bromoform and DBCM, and guideline values of 0.06 mg/litre for BDCM and 0.2 mg/litre for chloroform, associated with an upper-bound excess lifetime cancer risk of 10^{-5} , were derived. The guideline value of 0.2 mg/litre for chloroform was retained in the addendum to the second edition of the Guidelines, published

in 1998, but was developed on the basis of a TDI for threshold effects. These guideline values were brought forward to the third edition.

Assessment date

The risk assessment was conducted in 2004.

Principal references

IPCS (2000) *Disinfectants and disinfectant by-products*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 216).

IPCS (2004) *Chloroform*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 58).

WHO (2005) *Trihalomethanes in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/64).

12.122 Uranium

Uranium is widespread in nature, occurring in granites and various other mineral deposits. Uranium is used mainly as fuel in nuclear power stations. Uranium is present in the environment as a result of leaching from natural deposits, release in mill tailings, emissions from the nuclear industry, the combustion of coal and other fuels and the use of phosphate fertilizers that contain uranium. Intake of uranium through air is low, and it appears that intake through food is between 1 and 4 µg/day. Intake through drinking-water is normally extremely low; however, in circumstances in which uranium is present in a drinking-water source, the majority of intake can be through drinking-water.

Provisional guideline value	0.015 mg/litre The guideline value is designated as provisional because of outstanding uncertainties regarding the toxicology and epidemiology of uranium as well as difficulties concerning its technical achievability in smaller supplies.
Occurrence	Levels in drinking-water are generally less than 1 µg/litre, although concentrations as high as 700 µg/litre have been measured in private supplies.

12. CHEMICAL FACT SHEETS

TDI	0.6 µg/kg of body weight per day, based on the application of an uncertainty factor of 100 (for inter- and intraspecies variation) to a LOAEL (equivalent to 60 µg of uranium per kg of body weight per day) for degenerative lesions in the proximal convoluted tubule of the kidney in male rats in a 91-day study in which uranyl nitrate hexahydrate was administered in drinking-water. It was considered unnecessary to apply an additional uncertainty factor for the use of a LOAEL instead of a NOAEL and the short length of the study because of the minimal degree of severity of the lesions and the short half-life of uranium in the kidney, with no indication that the severity of the renal lesions will be exacerbated following continued exposure. This is supported by data from epidemiological studies.
Limit of detection	0.01 µg/litre by ICP/MS; 0.1 µg/litre by solid fluorimetry with either laser excitation or UV light; 0.2 µg/litre by ICP using adsorption with chelating resin
Treatment achievability	1 µg/litre should be achievable using conventional treatment, e.g., coagulation or ion exchange
Guideline derivation	
<ul style="list-style-type: none"> ● allocation to water ● weight ● consumption 	<p>80% of TDI (because intake from other sources is low in most areas)</p> <p>60-kg adult</p> <p>2 litres/day</p>
Additional comments	<ul style="list-style-type: none"> ● The data on intake from food in most areas suggest that intake from food is low and support the higher allocation to drinking-water. In some regions, exposure from sources such as soil may be higher and should be taken into account in setting national or local standards. ● The concentration of uranium in drinking-water associated with the onset of measurable tubular dysfunction remains uncertain, as does the clinical significance of the observed changes at low exposure levels. A guideline value of up to 30 µg/litre may be protective of kidney toxicity because of uncertainty regarding the clinical significance of changes observed in epidemiological studies. ● Only chemical, not radiological, aspects of uranium toxicity have been addressed here. ● A document on depleted uranium, which is a by-product of natural uranium, is available.

Toxicological review

There are insufficient data regarding the carcinogenicity of uranium in humans and experimental animals. Nephritis is the primary chemically induced effect of uranium in humans. Little information is available on the chronic health effects of exposure to environmental uranium in humans. A number of epidemiological studies of populations exposed to uranium in drinking-water have shown a correlation with alkaline phosphatase and β-microglobulin in urine along with modest alterations in proximal tubular function. However, the actual measurements were still within the normal physiological range.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to uranium. The 1971 *International Standards* stated that uranium should be controlled in drinking-water, but that insufficient information was available to enable a tentative limit to be established. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, it was concluded that no action was required for uranium. A health-based guideline value for uranium was not derived in the 1993 *Guidelines*, as adequate short- and long-term studies on the chemical toxicity of uranium were not available. Until such information became available, it was recommended that the limits for radiological characteristics of uranium be used. The equivalent for natural uranium, based on these limits, is approximately 0.14 mg/litre. In the addendum to the *Guidelines*, published in 1998, a health-based guideline value of 0.002 mg/litre was established. This guideline value was designated as provisional, because it may be difficult to achieve in areas with high natural uranium levels with the treatment technology available and because of limitations in the key study. It was noted that several human studies are under way that may provide helpful additional data.

Assessment date

The risk assessment was conducted in 2003.

Principal reference

WHO (2003) *Uranium in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/118).

12.123 Vinyl chloride

Vinyl chloride is used primarily for the production of PVC. Owing to its high volatility, vinyl chloride has rarely been detected in surface waters, except in contaminated areas. Unplasticized PVC is increasingly being used in some countries for water mains supplies. Migration of vinyl chloride monomer from unplasticized PVC is a possible source of vinyl chloride in drinking-water. It appears that inhalation is the most important route of vinyl chloride intake, although drinking-water may contribute a substantial portion of daily intake where PVC piping with a high residual content of vinyl chloride monomer is used in the distribution network. Vinyl chloride has been reported in groundwater as a degradation product of the chlorinated solvents trichloroethene and tetrachloroethene.

12. CHEMICAL FACT SHEETS

Guideline value	0.0003 mg/litre (0.3 µg/litre)
Occurrence	Rarely detected in surface waters, the concentrations measured generally not exceeding 10 µg/litre; much higher concentrations found in groundwater and well water in contaminated areas; concentrations up to 10 µg/litre detected in drinking-water
Basis for guideline derivation	Application of a linear extrapolation by drawing a straight line between the dose, determined using a pharmacokinetic model, resulting in tumours in 10% of animals in rat bioassays involving oral exposure and the origin (zero dose), determining the value associated with the upper-bound risk of 10^{-5} and assuming a doubling of the risk for exposure from birth
Limit of detection	0.01 µg/litre by GC with ECD or FID with MS for confirmation
Treatment achievability	0.001 mg/litre should be achievable using air stripping
Additional comments	<ul style="list-style-type: none"> • The results of the linear extrapolation are nearly identical to those derived using the linearized multistage model. • As vinyl chloride is a known human carcinogen, exposure to this compound should be avoided as far as practicable, and levels should be kept as low as technically feasible. • Vinyl chloride is primarily of concern as a potential contaminant from some grades of PVC pipe and is best controlled by specification of material quality.

Toxicological review

There is sufficient evidence of the carcinogenicity of vinyl chloride in humans from industrial populations exposed to high concentrations via the inhalation route, and IARC has classified vinyl chloride in Group 1. Studies of workers employed in the vinyl chloride industry have shown a marked exposure–response for all liver cancers, angiosarcomas and hepatocellular carcinoma, but no strong relationship between cumulative vinyl chloride exposure and other cancers. Animal data show vinyl chloride to be a multisite carcinogen. When administered orally or by inhalation to mice, rats and hamsters, it produced tumours in the mammary gland, lungs, Zymbal gland and skin, as well as angiosarcomas of the liver and other sites. Evidence indicates that vinyl chloride metabolites are genotoxic, interacting directly with DNA. DNA adducts formed by the reaction of DNA with a vinyl chloride metabolite have also been identified. Occupational exposure has resulted in chromosomal aberrations, micronuclei and sister chromatid exchanges; response levels were correlated with exposure levels.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to vinyl chloride. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline value was recommended, because the occurrence of vinyl chloride in water seemed to be associated primarily with the use of poorly polymerized PVC water pipes, a problem that was more appropriately controlled by product specification. The 1993 Guidelines calculated a guideline value of

0.005 mg/litre for vinyl chloride based on an upper-bound excess lifetime cancer risk of 10^{-5} .

Assessment date

The risk assessment was conducted in 2003.

Principal references

IPCS (1999) *Vinyl chloride*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 215).

WHO (2003) *Vinyl chloride in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/119).

12.124 Xylenes

Xylenes are used in blending petrol, as a solvent and as a chemical intermediate. They are released to the environment largely via air. Exposure to xylenes is mainly from air, and exposure is increased by smoking.

Guideline value	0.5 mg/litre
Occurrence	Concentrations of up to 8 µg/litre have been reported in surface water, groundwater and drinking-water; levels of a few milligrams per litre were found in groundwater polluted by point emissions. Xylenes can also penetrate plastic pipe from contaminated soil.
TDI	179 µg/kg of body weight, based on a NOAEL of 250 mg/kg of body weight per day for decreased body weight in a 103-week gavage study in rats, correcting for 5 days per week dosing and using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the limited toxicological end-points)
Limit of detection	0.1 µg/litre by GC/MS; 1 µg/litre by GC with FID
Treatment achievability	0.005 mg/litre should be achievable using GAC or air stripping
Guideline derivation	
● allocation to water	10% of TDI
● weight	60-kg adult
● consumption	2 litres/day
Additional comments	The guideline value exceeds the lowest reported odour threshold for xylenes in drinking-water.

Toxicological review

Xylenes are rapidly absorbed by inhalation. Data on oral exposure are lacking. Xylenes are rapidly distributed in the body, predominantly in adipose tissue. They are almost completely metabolized and excreted in urine. The acute oral toxicity of xylenes is low. No convincing evidence for teratogenicity has been found. Long-term carcino-

genicity studies have shown no evidence for carcinogenicity. *In vitro* as well as *in vivo* mutagenicity tests have proved negative.

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* and the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, did not refer to xylenes. The 1993 Guidelines proposed a health-based guideline value of 0.5 mg/litre for xylenes, noting that this value exceeds the lowest reported odour threshold for xylenes in drinking-water (0.02 mg/litre).

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Xylenes in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/25).

12.125 Zinc

Zinc is an essential trace element found in virtually all food and potable water in the form of salts or organic complexes. The diet is normally the principal source of zinc. Although levels of zinc in surface water and groundwater normally do not exceed 0.01 and 0.05 mg/litre, respectively, concentrations in tap water can be much higher as a result of dissolution of zinc from pipes.

In 1982, JECFA proposed a PMTDI for zinc of 1 mg/kg of body weight. The daily requirement for adult men is 15–20 mg/day. It was considered that, taking into account recent studies on humans, the derivation of a guideline value is not required at this time. However, drinking-water containing zinc at levels above 3 mg/litre may not be acceptable to consumers (see chapter 10).

History of guideline development

The 1958 WHO *International Standards for Drinking-water* suggested that concentrations of zinc greater than 15 mg/litre would markedly impair the potability of the water. The 1963 and 1971 *International Standards* retained this value as a maximum allowable or permissible concentration. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 5.0 mg/litre was established for zinc, based on taste considerations. The 1993 Guidelines concluded that, taking into account recent studies on humans, the derivation of a guideline value was not required at this time. However, drinking-water containing zinc at levels above 3 mg/litre may not be acceptable to consumers.

Assessment date

The risk assessment was originally conducted in 1993. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Zinc in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/17).

12.126 Pesticides used for vector control in drinking-water sources and containers

In setting local guidelines or standards in the context of local storage practices and realistic insecticide application regimes, health authorities should take into consideration the potential for higher rates of water consumption in the area or region under consideration. However, exceeding the ADIs will not necessarily result in adverse effects. The diseases spread by vectors are significant causes of morbidity and mortality. It is therefore important to achieve an appropriate balance between the intake of the pesticides from drinking-water and the control of disease-carrying insects. Better than establishing guideline values are the formulation and implementation of a comprehensive management plan for household water storage and peridomestic waste management that does not rely exclusively on larviciding by insecticides, but also includes other environmental management measures and social behavioural changes.

Formulations of pesticides used for vector control in drinking-water should strictly follow the label recommendations and should only be those approved for such a use by national authorities, taking into consideration the ingredients and formulants used in making the final product. National authorities should note that these assessments refer only to the active ingredients and do not consider the additives in different formulations.

12.126.1 Diflubenzuron

Diflubenzuron is a direct-acting insecticide normally applied directly to plants or water. It is used in public health applications against mosquito and noxious fly larvae. WHO is considering diflubenzuron for use as a mosquito larvicide in drinking-water in containers, particularly to control dengue fever. The recommended dosage of diflubenzuron in potable water in containers should not exceed 0.25 mg/litre under the WHO Pesticides Evaluation Scheme.

It is reported that public exposure to diflubenzuron through either food or drinking-water is negligible. However, there is a potential for direct exposure through drinking-water when diflubenzuron is directly applied to drinking-water storage containers.

Diflubenzuron is considered to be of very low acute toxicity. The primary target for toxicity is the erythrocytes, although the mechanism of haematotoxicity is uncertain. There is no evidence that diflubenzuron is either genotoxic or carcinogenic. It also does not appear to be fetotoxic or teratogenic and does not show significant signs of reproductive toxicity. There is evidence that young animals are not significantly more sensitive than adults to the effects of diflubenzuron.

It is not considered appropriate to set a formal guideline value for diflubenzuron used as a vector control agent in drinking-water. Where diflubenzuron is used for vector control in potable water, this will involve considerably less than lifetime exposure. The ADI determined by JMPR in 2001 was 0.02 mg/kg of body weight. The maximum dosage in drinking-water of 0.25 mg/litre would be equivalent to approximately 40% of the ADI allocated to drinking-water for a 60-kg adult drinking 2 litres of water per day. For a 10-kg child drinking 1 litre of water, the exposure would be 0.25 mg, compared with an exposure of 0.2 mg at the ADI. For a 5-kg bottle-fed infant drinking 0.75 litre per day, the exposure would be 0.19 mg, compared with an exposure of 0.1 mg at the ADI. Diflubenzuron is unlikely to remain in solution at the maximum recommended applied dose, and the actual levels of exposure are likely to be much lower than those calculated.

Consideration should be given to using alternative sources of water for bottle-fed infants for a period after an application of diflubenzuron, where this is practical. However, exceeding the ADI will not necessarily result in adverse effects.

History of guideline development

Diflubenzuron was not evaluated in the WHO *International Standards for Drinking-water* or in the first or second editions of the WHO *Guidelines for Drinking-water Quality*.

Assessment date

The risk assessment was conducted in 2007.

Principal references

FAO/WHO (2002) Diflubenzuron. In: *Pesticide residues in food – 2001 evaluations. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/02.1; <http://www.inchem.org/documents/jmpr/jmpmono/2001pr04.htm>).

WHO (2008) *Diflubenzuron in drinking-water: Use for vector control in drinking-water sources and containers. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/HSE/AMR/08.03/6).

12.126.2 Methoprene

WHO has assessed methoprene for use as a mosquito larvicide in drinking-water in containers, particularly to control dengue fever. The recommended dosage of methoprene in potable water in containers should not exceed 1 mg/litre under the WHO Pesticides Evaluation Scheme.

In 2001, JMPR reaffirmed the basis of the ADI for racemic methoprene established in 1987, but lowered the value to 0–0.09 mg/kg of body weight to correct for the purity of the racemate tested. The basis for the ADI was the NOAEL of 500 mg/kg, equivalent to 8.6 mg/kg of body weight per day (corrected for purity), in a 90-day study in dogs (the main effect was increased relative liver weight) and a safety factor of 100. Young animals do not appear to be significantly more sensitive than adults. As no bridging studies with repeated doses were available for (S)-methoprene, JMPR made the conservative assumption that, in the absence of any information to the contrary, all the toxicity of the racemate was due to the S enantiomer. On this basis, JMPR established an ADI for (S)-methoprene of 0–0.05 mg/kg of body weight, equal to one-half the ADI for the racemate (which is a 1:1 mixture of the R and S enantiomers).

It is not considered appropriate to set a formal guideline value for methoprene used as a vector control agent in drinking-water. Where methoprene is used for vector control in potable water, this will involve less than lifetime exposure. The maximum dosage in drinking-water of 1 mg/litre would be equivalent to approximately 66% of the ADI (0.033 mg/kg of body weight) for a 60-kg adult drinking 2 litres of water per day. The exposure for a 10-kg child drinking 1 litre of water would be approximately 0.1 mg/kg of body weight, and for a 5-kg bottle-fed infant, the exposure would be approximately 0.15 mg/kg of body weight, compared with the ADI of 0–0.05 mg/kg of body weight. However, the low solubility and the high log K_{ow} of methoprene indicate that it is unlikely to remain in solution at the maximum recommended applied dose, and the actual levels of exposure are likely to be much lower than those calculated. Exposure from food is considered to be low.

Consideration should be given to using alternative sources of water for small children and bottle-fed infants for a period after an application of methoprene, where this is practical. However, exceeding the ADI will not necessarily result in adverse effects.

History of guideline development

Methoprene was not considered in the WHO *International Standards for Drinking-water* or in the first or second editions of the WHO *Guidelines for Drinking-water Quality*.

Assessment date

The risk assessment was conducted in 2007.

Principal references

- FAO/WHO (2002) Methoprene and S-methoprene. In: *Pesticide residues in food – 2001 evaluations. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/02.1; <http://www.inchem.org/documents/jmpr/jmpmono/2001pr09.htm>).
- WHO (2008) *Methoprene in drinking-water: Use for vector control in drinking-water sources and containers. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/HSE/AMR/08.03/14).

12.126.3 Novaluron

Novaluron has been registered as an insecticide for food crops and ornamentals in a number of countries. WHO has assessed novaluron for use as a mosquito larvicide in drinking-water in containers, particularly to control dengue fever. The recommended dosage of novaluron in potable water in containers should not exceed 0.05 mg/litre under the WHO Pesticides Evaluation Scheme.

In view of the absence of a carcinogenic potential in rodents and the lack of genotoxic potential *in vitro* and *in vivo*, JMPR concluded that novaluron is unlikely to pose a carcinogenic risk to humans. JMPR also concluded that novaluron is not a developmental toxicant.

JMPR established an ADI of 0–0.01 mg/kg of body weight on the basis of the NOAEL of 1.1 mg/kg of body weight per day for erythrocyte damage and secondary splenic and liver changes in a 2-year dietary study in rats, and a safety factor of 100.

It is not considered appropriate to set a formal guideline value for novaluron as a vector control agent in drinking-water. At the maximum recommended dosage for drinking-water of 0.05 mg/litre, the intake of a 60-kg adult drinking 2 litres of water would represent only 17% of the ADI. Similarly, the intake for a 10-kg child drinking 1 litre of water would be 50% of the ADI, whereas a 5-kg bottle-fed infant drinking 0.75 litre of water would receive an intake of 75% of the ADI.

The high log K_{ow} of 4.3 indicates that novaluron is likely to adsorb to the sides of containers, and so the actual concentration is likely to be less than the recommended dose. Exposure to novaluron through food is not expected to be significant.

History of guideline development

Novaluron was not considered in the WHO *International Standards for Drinking-water* or in the first or second editions of the WHO *Guidelines for Drinking-water Quality*.

Assessment date

The risk assessment was conducted in 2007.

Principal references

- FAO/WHO (2005) Novaluron. In: *Pesticide residues in food – 2005*. Rome, Food and Agriculture Organization of the United Nations, Joint FAO/WHO Meeting on Pesticide Residues (FAO Plant Production and Protection Paper 183; http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/2005_rep/report2005jmpr.pdf).
- WHO (2008) *Novaluron in drinking-water: Use for vector control in drinking-water sources and containers. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/HSE/AMR/08.03/11).

12.126.4 Pirimiphos-methyl

Pirimiphos-methyl is an organophosphorus compound that is used in a wide range of pesticidal applications. Pirimiphos-methyl is being considered by WHO for addition to potable water in containers as a mosquito larvicide treatment, particularly to control dengue fever. The manufacturer recommends the direct addition of 1 mg/litre to water.

The only biochemical effect consistently observed with pirimiphos-methyl in acute, short-term or long-term studies is cholinesterase inhibition. Studies with mice, rats and dogs showed NOAELs of 0.5 mg/kg of body weight per day and above. Young animals do not appear to be significantly more sensitive than adults. In human studies, no cholinesterase inhibition was seen at 0.25 mg/kg of body weight per day (the highest dose tested). On this basis, JMPR revised the ADI to 0–0.03 mg/kg of body weight by applying a 10-fold safety factor to the NOAEL in the human studies.

At the maximum recommended dosage for drinking-water of 1 mg/litre, a 60-kg adult drinking 2 litres of water would have an intake of 0.033 mg/kg of body weight, compared with the ADI of 0–0.03 mg/kg of body weight. The intake for a 10-kg child drinking 1 litre of water would be 0.1 mg/kg of body weight; for a 5-kg bottle-fed infant drinking 0.75 litre, it would be 0.15 mg/kg of body weight. There is uncertainty regarding the level that would cause effects in humans, since the NOAEL on which the ADI is based was the highest dose tested, and so the ADI may be more conservative than is at first apparent. These intake figures are all below the ARfD of 0.2 mg/kg of body weight and would not result in an acute exposure risk from the initial application of pirimiphos-methyl to drinking-water containers at the recommended dose. In addition, the low solubility and the high $\log K_{ow}$ of pirimiphos-methyl indicate that it is very unlikely to remain in solution at the maximum recommended applied dose, so the actual levels of exposure are expected to be lower than those calculated. Exposure from food is generally considered to be low, but occasional high exposures can be experienced.

Based on the above calculations, pirimiphos-methyl is not recommended for direct application to drinking-water unless no other effective and safe treatments are available. If pirimiphos-methyl is applied directly to drinking-water, consideration should

be given to using alternative sources of water for bottle-fed infants and small children for a period after its application, where this is practical. However, it is noted that exceeding the ADI will not necessarily result in adverse effects.

History of guideline development

Pirimiphos-methyl was not considered in the WHO *International Standards for Drinking-water* or in the first or second editions of the WHO *Guidelines for Drinking-water Quality*.

Assessment date

The risk assessment was conducted in 2007.

Principal references

FAO/WHO (1993) Pirimiphos-methyl. In: *Pesticide residues in food – 1992 evaluations. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/93.34; <http://www.inchem.org/documents/jmpr/jmpmono/v92pr16.htm>).

FAO/WHO (2006) Pirimiphos-methyl. In: *Pesticide residues in food 2006*. Rome, Food and Agriculture Organization of the United, Joint FAO/WHO Meeting on Pesticide Residues, pp. 178–179 (FAO Plant Production and Protection Paper 187; http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/2006_rep/report2006jmp.pdf).

WHO (2008) *Pirimiphos-methyl in drinking-water: Use for vector control in drinking-water sources and containers. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/HSE/AMR/08.03/15).

12.126.5 Pyriproxyfen

Pyriproxyfen is a broad-spectrum insect growth regulator with insecticidal activity against public health insect pests, including mosquitoes. WHO has assessed pyriproxyfen for use as a mosquito larvicide in drinking-water in containers, particularly to control dengue fever. The recommended dosage of pyriproxyfen in potable water in containers should not exceed 0.01 mg/litre under the WHO Pesticides Evaluation Scheme.

JMPR evaluated pyriproxyfen and concluded that it was not genotoxic and does not pose a carcinogenic risk to humans. Young animals do not appear to be significantly more sensitive than adults.

JMPR established an ADI of 0–0.1 mg/kg of body weight on the basis of an overall NOAEL of 10 mg/kg of body weight per day, based on increased relative liver weight and increased total plasma cholesterol concentration in male dogs in two 1-year studies of toxicity and a safety factor of 100.

It is not considered appropriate to set a formal guideline value for pyriproxyfen used for vector control in drinking-water. The maximum recommended dosage in drinking-water of 0.01 mg/litre would be equivalent to less than 1% of the ADI allocated to drinking-water for a 60-kg adult drinking 2 litres of water per day. For a 10-kg child drinking 1 litre of water, the exposure would be 0.01 mg, compared with an exposure of 1 mg at the ADI. For a 5-kg bottle-fed infant drinking 0.75 litre per day, the exposure would be 0.0075 mg, compared with an exposure of 0.5 mg at the ADI. The low solubility and the high $\log K_{ow}$ of pyriproxyfen indicate that it is unlikely to remain in solution at the maximum recommended applied dose, and the actual levels of exposure are likely to be even lower than those calculated.

A guideline value for pyriproxyfen used for agriculture purposes is described in section 12.104.

History of guideline development

The 1958 and 1963 WHO *International Standards for Drinking-water* did not refer to pyriproxyfen, but the 1971 International Standards suggested that pesticide residues that may occur in community water supplies make only a minimal contribution to the total daily intake of pesticides for the population served. Pyriproxyfen was not evaluated in the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, in the second edition, published in 1993, or in the addendum to the second edition, published in 1998. A guideline value for pyriproxyfen was published in the third edition. It was subsequently decided to evaluate pyriproxyfen as a vector control larvicide separately from its other uses.

Assessment date

The risk assessment was conducted in 2007.

Principal references

- FAO/WHO (2000) Pyriproxyfen. In: *Pesticide residues in food – 1999 evaluations. Part II – Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/00.4; <http://www.inchem.org/documents/jmpr/jmpmono/v99pr12.htm>).
- WHO (2008) *Pyriproxyfen in drinking-water: Use for vector control in drinking-water sources and containers. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/HSE/AMR/08.03/9).