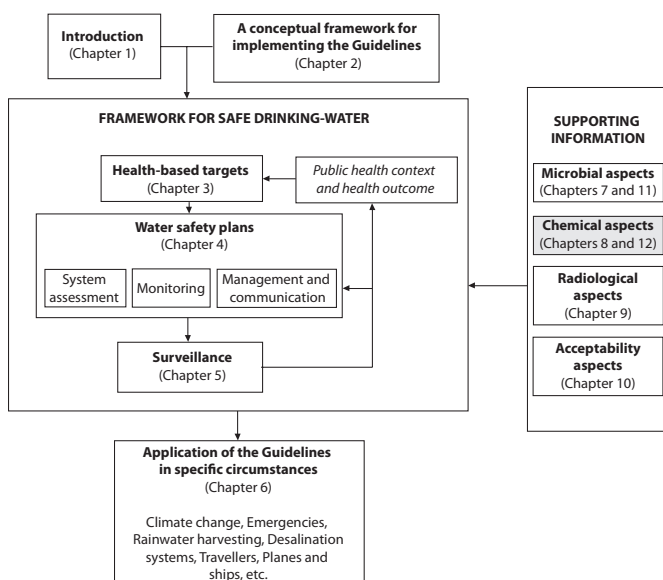


# 12

## Chemical fact sheets

The background documents referred to in this chapter (as the principal reference for each fact sheet) may be found on the Water, Sanitation, Hygiene and Health web site at [http://www.who.int/water\\_sanitation\\_health/dwq/chemicals/en/index.html](http://www.who.int/water_sanitation_health/dwq/chemicals/en/index.html). A complete list of references cited in this chapter, including the background documents for each chemical, is provided in Annex 2.



### 12.1 Chemical contaminants in drinking-water

#### **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/l. At a monomer content of 0.05%, this corresponds to a maximum theoretical concentration of 0.5 µg/l 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. Human exposure is much greater from food than from drinking-water, owing to the formation of acrylamide in foods (e.g. breads, fried and roasted foods) cooked at high temperatures.

## GUIDELINES FOR DRINKING-WATER QUALITY

Guideline value	0.0005 mg/l (0.5 µg/l)
Occurrence	Concentrations up to a few micrograms per litre occasionally detected in tap water
Basis of guideline value 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/l by gas chromatography (GC); 0.2 µg/l by high-performance liquid chromatography (HPLC); 10 µg/l by HPLC with ultraviolet (UV) detection
Treatment performance	Conventional treatment processes do not remove acrylamide. Acrylamide concentrations in drinking-water are usually controlled by limiting either the acrylamide content of polyacrylamide flocculants or the dose used, or both. Advances in analytical techniques are also beginning to allow control by direct measurement (see background document).
Additional comments	Every effort should be made to limit free acrylamide monomer in polyacrylamide used for water treatment, and water suppliers should also make every effort to ensure that residual acrylamide in drinking-water is kept as low as is technically feasible. In particular, if acrylamide is controlled by limiting the amount dosed, overdosing should always be avoided.
Assessment date	2011
Principal references	FAO/WHO (2011) <i>Evaluation of certain contaminants in food</i> WHO (2011) <i>Acrylamide in drinking-water</i>

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. The International Agency for Research on Cancer (IARC) has placed acrylamide in Group 2A (probably carcinogenic to humans). The Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) has recently noted concerns regarding the carcinogenicity and neurotoxicity of acrylamide and concluded that dietary exposure should be reduced to as low a level as technically achievable. Recent data have shown that exposure to acrylamide from cooked food is much higher than previously thought. As it is difficult to control the intake of acrylamide from food, it is very important that the acrylamide content of polyacrylamide used as a coagulant aid in water treatment, the most important source of drinking-water contamination by acrylamide, be as low as possible and that polyacrylamide not be overdosed in an attempt to take a shortcut to improving coagulation.

### **Alachlor**

Alachlor (Chemical Abstracts Service [CAS] No. 15972-60-8) is a pre-emergence and post-emergence herbicide used to control annual grasses and many broad-leaved weeds

## 12. CHEMICAL FACT SHEETS

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. Alachlor was included in the Prior Informed Consent procedure of the Rotterdam Convention on the basis of the final regulatory actions taken by the European Community and by Canada to ban alachlor as a pesticide.

Guideline value	0.02 mg/l (20 µg/l)
Occurrence	Has been detected in groundwater and surface water; has also been detected in drinking-water at levels below 0.002 mg/l
Basis of guideline value derivation	Calculated by applying the linearized multistage model to data on the incidence of nasal tumours in rats
Limit of detection	0.1 µg/l by gas-liquid chromatography with electrolytic conductivity detection in the nitrogen mode or by capillary column GC with a nitrogen-phosphorus detector
Treatment performance	0.001 mg/l should be achievable using granular activated carbon (GAC)
Assessment date	1993
Principal reference	WHO (2003) <i>Alachlor in drinking-water</i>

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.

### **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.

Guideline value	0.01 mg/l (10 µg/l)
Occurrence	Frequently found as a contaminant in groundwater in the vicinity of application areas, particularly when associated with sandy soil; concentrations in well water as high as 500 µg/l have been measured; aldicarb sulfoxide and aldicarb sulfone residues are found in an approximately 1:1 ratio in groundwater
Acceptable daily intake (ADI)	0–0.003 mg/kg body weight based on cholinesterase depression in a single oral dose study in human volunteers
Limit of detection	0.001 mg/l by reversed-phase HPLC with fluorescence detection
Treatment performance	0.001 mg/l should be achievable using GAC or ozonation
Guideline value derivation	
• allocation to water	10% of upper limit of ADI
• weight	60 kg adult
• consumption	2 litres/day

Additional comments	The guideline value derived from the 1992 assessment of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) was very similar to the guideline value derived in the second edition, which was therefore retained.
Assessment date	2003
Principal references	FAO/WHO (1993) <i>Pesticide residues in food—1992 evaluations</i> WHO (2003) <i>Aldicarb in drinking-water</i>

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 converted to the sulfoxide and sulfone. Aldicarb sulfoxide is a more potent inhibitor of acetylcholinesterase than aldicarb itself, whereas 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).

### **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, many 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	<i>Aldrin and dieldrin (combined):</i> 0.000 03 mg/l (0.03 µg/l)
Occurrence	Seldom detected in drinking-water; concentrations of aldrin and dieldrin in drinking-water normally less than 0.01 µg/l; rarely present in groundwater
Provisional tolerable daily intake (PTDI)	0.1 µg/kg body weight (combined total for aldrin and dieldrin), based on no-observed-adverse-effect levels (NOAELs) of 1 mg/kg diet in the dog and 0.5 mg/kg diet in the rat, which are equivalent to 0.025 mg/kg 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/l for aldrin and 0.002 µg/l for dieldrin by GC with electron capture detector (ECD)
Treatment performance	0.02 µg/l should be achievable using coagulation, GAC or ozonation
Guideline value derivation	<ul style="list-style-type: none"> <li>• allocation to water 1% of PTDI (In view of the reduction in exposure from food, this value is probably very conservative.)</li> <li>• weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>

## 12. CHEMICAL FACT SHEETS

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.
Assessment date	2003
Principal references	FAO/WHO (1995) <i>Pesticide residues in food—1994 evaluations</i> WHO (2003) <i>Aldrin and dieldrin in drinking-water</i>

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 (not classifiable as to its carcinogenicity to humans). Exposure through food has decreased significantly with the dramatic reduction in use.

### **Aluminium**

Aluminium is the most abundant metallic element and constitutes about 8% of 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.

Reason for not establishing a guideline value	A health-based value of 0.9 mg/l could be derived from the JECFA provisional tolerable weekly intake (PTWI), but this value exceeds practicable levels based on optimization of the coagulation process in drinking-water plants using aluminium-based coagulants: 0.1 mg/l or less in large water treatment facilities and 0.2 mg/l or less in small facilities
Assessment date	2009
Principal references	FAO/WHO (2007) <i>Aluminium</i> (from all sources, including food additives) IPCS (1997) <i>Aluminium</i> WHO (2010) <i>Aluminium in drinking-water</i>

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 in humans. The 1997 WHO Environmental Health Criteria document for aluminium concludes that:

On the whole, the positive relationship between aluminium in drinking-water and AD [Alzheimer disease], 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/l, 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.

In 2007, JECFA developed a PTWI for aluminium from all sources of 1 mg/kg body weight. JECFA concluded the following:

... the available studies have many limitations and are not adequate for defining the dose-response relationships. The Committee therefore based its evaluation on the combined evidence from several studies. The relevance of studies involving administration of aluminium compounds by gavage was unclear because the toxicokinetics after gavage were expected to differ from toxicokinetics after dietary administration, and the gavage studies generally did not report total aluminium exposure including basal levels in the feed. The studies conducted with dietary administration of aluminium compounds were considered most appropriate for the evaluation. The lowest LOELs [lowest-observed-effect levels] for aluminium in a range of different dietary studies in mice, rats and dogs were in the region of 50–75 mg/kg bw [body weight] per day expressed as Al.

The Committee applied an uncertainty factor of 100 to the lower end of this range of LOELs (50 mg/kg bw per day expressed as Al) to allow for inter- and intraspecies differences. There are deficiencies in the database, notably the absence of NOELs [no-observed-effect levels] in the majority of the studies evaluated and the absence of long-term studies on the relevant toxicological end-points. The deficiencies are counterbalanced by the probable lower bioavailability of the less soluble aluminium species present in food. Overall, an additional uncertainty factor of three was considered to be appropriate. The Committee confirmed that the resulting health-based guidance value should be expressed as a PTWI, because of the potential for bioaccumulation. The Committee established a PTWI of 1 mg/kg bw for Al, which applies to all aluminium compounds in food, including additives.

A health-based value derived from the JECFA PTWI would be 0.9 mg/l (rounded value), based on an allocation of 20% of the PTWI to drinking-water and assuming a 60 kg adult drinking 2 litres of water per day. However, there remain uncertainties as to the extent of aluminium absorption from drinking-water, which depends on a number of parameters, such as the aluminium salt administered, pH (for aluminium speciation and solubility), bioavailability and dietary factors.

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/l 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/l or less is a practicable level for aluminium in finished water.

As indicated above, a health-based value derived from the JECFA PTWI would be 0.9 mg/l (rounded value) based on an allocation of 20% of the PTWI to drinking-water and assuming a 60 kg adult drinking 2 litres of water per day. However, as also noted above, practicable levels based on optimization of the coagulation process in drinking-water plants using aluminium-based coagulants are less than 0.1 mg/l in large water treatment facilities and less than 0.2 mg/l in small facilities. In view of the importance of optimizing coagulation to prevent microbial contamination and the need to minimize deposition of aluminium floc in distribution systems, it is important to ensure that average residuals do not exceed these values.

### **Ammonia**

The term ammonia includes the non-ionized ( $\text{NH}_3$ ) and ionized ( $\text{NH}_4^+$ ) 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/l. Anaerobic groundwaters may contain up to 3 mg/l. 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.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	1993
Principal reference	WHO (2003) <i>Ammonia in drinking-water</i>

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 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).

**Antimony**

Elemental antimony forms very hard alloys with copper, lead and tin. Antimony compounds have various therapeutic uses. Antimony is used in solders as a replacement for lead, but there is little evidence of any significant contribution to drinking-water concentrations from this source. Total exposure from environmental sources, food and drinking-water is very low compared with occupational exposure.

Guideline value	0.02 mg/l (20 µg/l)
Occurrence	Concentrations in groundwater less than 0.001 µg/l; concentrations in surface water less than 0.2 µg/l; concentrations in drinking-water appear to be less than 5 µg/l
Tolerable daily intake (TDI)	6 µg/kg body weight, based on a NOAEL of 6.0 mg/kg 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 interspecies and intraspecies variation, 10 for the short duration of the study)
Limit of detection	0.01 µg/l by electrothermal atomic absorption spectrometry (AAS); 0.1–1 µg/l by inductively coupled plasma mass spectrometry (ICP-MS); 0.8 µg/l by graphite furnace AAS; 5 µg/l by hydride generation AAS
Treatment performance	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 value derivation	<ul style="list-style-type: none"> <li>● allocation to water 10% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
Assessment date	2003
Principal reference	WHO (2003) <i>Antimony in drinking-water</i>

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, owing 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, as 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.

### **Arsenic<sup>1</sup>**

Arsenic is found widely in 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/l. 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/l 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/l (10 µg/l) The guideline value is designated as provisional on the basis of treatment performance and analytical achievability.
Occurrence	Levels in natural waters generally range between 1 and 2 µg/l, although concentrations may be elevated (up to 12 mg/l) in areas containing natural sources
Basis of guideline value 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 practical difficulties in removing arsenic from drinking-water, as well as the practical quantification limit in the region of 1–10 µg/l, the guideline value of 10 µg/l is retained and designated as provisional.
Limit of detection	0.1 µg/l by ICP-MS; 2 µg/l by hydride generation AAS or flame AAS
Treatment performance	It is technically feasible to achieve arsenic concentrations of 5 µg/l 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/l should be achievable by conventional treatment (e.g. coagulation).

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

Assessment date	2011
Principal references	FAO/WHO (2011) <i>Evaluation of certain contaminants in food</i> IARC (1987) <i>Overall evaluations of carcinogenicity</i> IPCS (2001) <i>Arsenic and arsenic compounds</i> ISO (1982) <i>Water quality—determination of total arsenic</i> USNRC (2001) <i>Arsenic in drinking water, 2001 update</i> WHO (2011) <i>Arsenic in drinking-water</i>

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 monomethylated, dimethylated 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/l) of arsenic has been reported.

Signs of chronic arsenicism, including dermal lesions such as hyperpigmentation 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/l) 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. The International Programme on Chemical Safety (IPCS) 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 below 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 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. In its updated evaluation, the United States National Research Council 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 of America (USA) exposed to arsenic at concentrations of 10 µg/l 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/l 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/l, and removal of arsenic to concentrations below 10 µg/l is difficult in many circumstances. In view of the practical difficulties in removing arsenic from drinking-water, particularly from small supplies, and the practical quantification limit for arsenic, the guideline value of 10 µg/l is retained as a goal and designated as provisional.

The provisional guideline value of 10 µg/l was previously supported by a JECFA PTWI of 15 µg/kg body weight, assuming an allocation of 20% to drinking-water. However, JECFA recently re-evaluated arsenic and concluded that the existing PTWI was very close to the lower confidence limit on the benchmark dose for a 0.5% response (BMDL<sub>0.5</sub>) calculated from epidemiological studies and was therefore no longer appropriate. The PTWI was therefore withdrawn. Nevertheless, given that, in many countries, even the provisional guideline value may not be attainable, it is retained on

the basis of treatment performance and analytical achievability with the proviso that every effort should be made to keep concentrations as low as reasonably possible.

### Practical considerations

A silver diethyldithiocarbamate spectrophotometric method (ISO 6595:1982) is available for the determination of arsenic; the detection limit is about 1 µg/l. 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/l 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/l should be achievable by conventional treatment (e.g. coagulation). For local non-piped water supplies, the first option is often substitution by, or dilution with, microbially 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.

### 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.

Reason for not establishing a guideline value	No consistent evidence that ingested asbestos is hazardous to health
Assessment date	1993
Principal reference	WHO (2003) <i>Asbestos in drinking-water</i>

Asbestos is a known human carcinogen by the inhalation route. Although it has been well studied, there is 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 experimental 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. The primary issue surrounding asbestos-cement pipes is for people working on the outside of the pipes (e.g. cutting pipe), because of the risk of inhalation of asbestos dust.

**Atrazine and its metabolites**

Atrazine is a selective systemic herbicide of the chlorotriazine class, used for the control of annual broadleaf and grassy weeds. Atrazine and its chloro-*s*-triazine metabolites—deethyl-atrazine, deisopropyl-atrazine and diaminochlorotriazine—have been found in surface water and groundwater as a result of the use of atrazine as a pre-emergent or early post-emergent herbicide. The metabolite hydroxyatrazine is more commonly detected in groundwater than in surface water.

Guideline values	<i>Atrazine and its chloro-s-triazine metabolites</i> : 0.1 mg/l (100 µg/l) <i>Hydroxyatrazine</i> : 0.2 mg/l (200 µg/l)
Occurrence	Concentrations rarely exceed 2 µg/l and are commonly well below 0.1 µg/l
Group ADI for atrazine and its chloro- <i>s</i> -triazine metabolites	0–0.02 mg/kg body weight based on the NOAEL for atrazine of 1.8 mg/kg body weight per day identified on the basis of luteinizing hormone surge suppression and subsequent disruption of the estrous cycle seen at 3.6 mg/kg body weight per day in a 6-month study in rats, using a safety factor of 100
ADI for hydroxyatrazine	0–0.04 mg/kg body weight based on the NOAEL of 1.0 mg/kg body weight per day identified on the basis of kidney toxicity at 7.8 mg/kg body weight per day in a 24-month study in rats, using a safety factor of 25, based on kinetic considerations
Limit of detection	<i>Atrazine</i> : 1 ng/l, isotope dilution MS with solid-phase extraction; 10 ng/l, GC-MS with solid-phase extraction; 50 ng/l, liquid chromatography (LC)-MS with solid-phase extraction; 100 ng/l, GC with nitrogen-phosphorus detection  <i>Metabolites</i> : 5 ng/l, capillary GC with nitrogen thermionic specific detection and HPLC with photodiode array absorption detection following extraction with styrene-divinylbenzene sorbents and elution with acetone
Treatment performance	0.1 µg/l can be achieved using GAC or powdered activated carbon (PAC); bankside filtration and nanofiltration are also effective
Guideline value derivation	<ul style="list-style-type: none"> <li>• allocation to water 20% of upper limit of ADI</li> <li>• body weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>
Additional comments	JMPR considered that the NOAEL for atrazine is protective for the consequences of neuroendocrine and other adverse effects caused by prolonged exposure to atrazine and its chloro- <i>s</i> -triazine metabolites.  JMPR was not able to assess the source allocation of atrazine to drinking-water. As such, the default 20% allocation was chosen, as it will be very conservative in most countries; in addition, it is expected that exposure of the public will be primarily through drinking-water.
Assessment date	2011
Principal references	FAO/WHO (2009) <i>Pesticide residues in food—2007 evaluations</i> WHO (2011) <i>Atrazine and its metabolites in drinking-water</i>

JMPR agreed that it is unlikely that atrazine is genotoxic and concluded that atrazine is not likely to pose a carcinogenic risk to humans, as the mode of carcinogenic action in certain susceptible rat strains is not relevant for human risk assessment. The weight of evidence from the epidemiological studies also did not support a causal association between exposure to atrazine and the occurrence of cancer in humans.

In special studies of reproductive toxicity, exposure of rats during early pregnancy (i.e. the luteinizing hormone–dependent period) caused increased pre-implantation or post-implantation losses, including full-litter resorptions. Attenuation of the luteinizing hormone surge and subsequent disruption of the estrous cycle (characterized by an increase in days in estrus) were observed at and above 3.65 mg/kg body weight per day, with a NOAEL of 1.8 mg/kg body weight per day. The effects on the luteinizing hormone surge and disruption of the estrous cycle were further supported by a number of short-term mechanistic studies. Additional experiments suggested that the effects of atrazine on luteinizing hormone and prolactin secretion are mediated via a hypothalamic site of action. JMPR concluded that atrazine was not teratogenic.

Studies using a variety of test systems *in vitro* and *in vivo* indicated that modulation of the immune system occurs after exposure to atrazine. However, effects suggestive of impaired function of the immune system were observed only at doses greater than those shown to affect neuroendocrine function, leading to disruption of the estrous cycle or developmental effects.

The toxicity profiles and mode of action of the chloro-*s*-triazine metabolites are similar to those of atrazine; the potency of these metabolites with regard to their neuroendocrine-disrupting properties appeared to be similar to that of the parent compound.

The metabolite hydroxyatrazine does not have the same mode of action or toxicity profile as atrazine and its chloro-*s*-triazine metabolites. The main effect of hydroxyatrazine was kidney toxicity (owing to its low solubility in water, resulting in crystal formation and a subsequent inflammatory response), and there was no evidence that hydroxyatrazine has neuroendocrine-disrupting properties. There was no evidence of carcinogenicity, and hydroxyatrazine did not show genotoxicity in an adequate range of tests *in vitro* and *in vivo*.

### **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/l (700 µg/l)
Occurrence	Concentrations in drinking-water generally below 100 µg/l, although concentrations above 1 mg/l have been measured in drinking-water derived from groundwater

## 12. CHEMICAL FACT SHEETS

NOAEL in humans	7.3 mg/l 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 barium at a mean concentration of 7.3 mg/l and one whose water contained barium at a concentration of 0.1 mg/l
Basis of guideline value derivation	Uncertainty factor of 10 for intraspecies variation applied to NOAEL in humans
Limit of detection	0.1 µg/l by ICP-MS; 2 µg/l by AAS; 3 µg/l by ICP-optical emission spectroscopy
Treatment performance	0.1 mg/l 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.
Assessment date	2003
Principal references	IPCS (2001) <i>Barium and barium compounds</i> WHO (2003) <i>Barium in drinking-water</i>

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.

### **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.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	FAO/WHO (1999) <i>Pesticide residues in food—1998 evaluations</i> WHO (2003) <i>Bentazone in drinking-water</i>

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/l can be calculated on the basis of

an ADI of 0–0.1 mg/kg 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 of health concern, it is not considered necessary to derive a health-based guideline value.

### **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/l (10 µg/l)
Occurrence	Concentrations in drinking-water, when present, generally much less than 5 µg/l
Basis of guideline value 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
Limit of detection	0.2 µg/l by GC with photoionization detection and confirmation by MS
Treatment performance	0.01 mg/l 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/l) 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.
Assessment date	1993
Principal reference	WHO (2003) <i>Benzene in drinking-water</i>

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 experimental 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.

### **Beryllium**

The primary source of beryllium compounds in water appears to be release from coal burning and other industries using beryllium. Other sources of beryllium in surface water include deposition of atmospheric beryllium and weathering of rocks and soils



containing beryllium. Beryllium is not likely to be found in natural water above trace levels as a result of the insolubility of beryllium oxides and hydroxides in the normal pH range.

Reason for not establishing a guideline value	Rarely found in drinking-water at concentrations of health concern
Assessment date	2009
Principal references	IPCS (2001) <i>Beryllium and beryllium compounds</i> WHO (2009) <i>Beryllium in drinking-water</i>

As beryllium is rarely, if ever, found in drinking-water at concentrations of concern, it is not considered necessary to set a formal guideline value.

A health-based value for beryllium in drinking-water of 12 µg/l can be calculated based on an allocation of 20% of the TDI of 2 µg/kg body weight, derived from a long-term study in which dogs exhibited lesions of the small intestine, to drinking-water and assuming a 60 kg adult drinking 2 litres of water per day. This allocation is probably conservative, as the limited data on food indicate that exposure from this source is likely to be well below the TDI.

Although beryllium appears to be found in drinking-water sources and drinking-water at low concentrations, the database on occurrence is limited, and there may be specific circumstances in which concentrations can be elevated due to natural sources where the pH is either below 5 or above 8 or there is high turbidity.

### **Boron**

Boron compounds are used in the manufacture of glass, soaps and detergents and as flame retardants. Naturally occurring boron is present in groundwater primarily as a result of leaching from rocks and soils containing borates and borosilicates. The borate content of surface water can be increased as a result of wastewater discharges, but this use has decreased significantly, and levels of boron in wastewater discharges continue to fall.

Guideline value	2.4 mg/l (2400 µg/l)
Occurrence	Concentrations vary widely and depend on the surrounding geology and wastewater discharges; for most of the world, the concentration of boron in drinking-water is judged to be below 0.5 mg/l
TDI	0.17 mg/kg body weight, based on a BMDL <sub>05</sub> of 10.3 mg/kg 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	0.15 µg/l by ICP-MS; 6–10 µg/l by ICP-atomic emission spectrometry (AES)
Treatment performance	Conventional water treatment (coagulation, sedimentation, filtration) does not significantly remove boron, and special methods need to be used 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 value derivation	
• allocation to water	40% of TDI (because intake from other sources is low)
• body weight	60 kg adult
• consumption	2 litres/day
Additional comments	Because it will be difficult to achieve the guideline value of 2.4 mg/l in some desalinated supplies and in areas with high natural boron levels, local regulatory and health authorities should consider a value in excess of 2.4 mg/l by assessing exposure from other sources.
Assessment date	2009
Principal reference	WHO (2009) <i>Boron in drinking-water</i>

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.

### **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 has also been 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 can occur as a result of pollution from industrial sources, sometimes as a consequence of its presence in contaminated soil. However, the main source in drinking-water is its formation during ozonation when the bromide ion is present in water. Bromate may also be formed in hypochlorite solutions produced by electrolysis of bromide-containing salt.

Provisional guideline value	0.01 mg/l (10 µg/l) 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 less than 2 to 293 µg/l, 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 value derivation	Upper-bound estimate of cancer potency for bromate is 0.19 per mg/kg 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/l is associated with the upper-bound excess cancer risk of 10 <sup>-5</sup> . A similar conclusion may be reached through several other methods of extrapolation, leading to values in the range 2–6 µg/l.

## 12. CHEMICAL FACT SHEETS

Limit of detection	0.2 µg/l by ion chromatography with UV/visible absorbance detection; 0.3 µg/l by ion chromatography with detection by ICP-MS; 1.5 µg/l by ion chromatography with suppressed conductivity detection
Treatment performance	Bromate is difficult to remove once formed. By appropriate control of disinfection conditions, it is possible to achieve bromate concentrations below 0.01 mg/l.
Assessment date	2003
Principal reference	WHO (2003) <i>Bromate in drinking-water</i>

IARC has concluded that although there is inadequate evidence of carcinogenicity in humans, there is sufficient evidence for the carcinogenicity of bromate from high-dose studies in experimental animals; IARC has classified bromate 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 as to the mode of carcinogenic action for 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 oxidative deoxyribonucleic acid (DNA) damage. Although there is 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 the induction of kidney tumours. However, emerging evidence points to rapid decomposition of bromate in the gastrointestinal tract, blood and liver, which supports a non-linear dose–response relationship at low doses.

### **Bromide**

Bromide is commonly found in nature along with sodium chloride, owing to their similar physical and chemical properties, but in smaller quantities. Bromide concentrations in seawater range from 65 mg/l to well over 80 mg/l, in fresh water from trace amounts to about 0.5 mg/l and in desalinated waters up to 1 mg/l.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2009
Principal reference	WHO (2009) <i>Bromide in drinking-water</i>

Inorganic bromide was evaluated in 1966 by JMPR, which recommended an ADI of 0–1 mg/kg body weight, based on a minimum pharmacologically effective dosage in humans of about 900 mg of potassium bromide, equivalent to 600 mg of bromide ion. The JMPR ADI was reaffirmed with new data in 1988.

The results of human studies suggest a conservative no-observed-effect level (NOEL) (for marginal effect within normal limits of electroencephalograms in

females) of 4 mg/kg body weight per day, giving an ADI of 0–0.4 mg/kg body weight, including a safety factor of 10 for population diversity.

The upper limit of the ADI of 0–0.4 mg/kg body weight yields an acceptable total daily intake of 24 mg/person for a 60 kg person. Assuming a relative source contribution of 50%, the drinking-water value for a 60 kg adult consuming 2 litres/day would be up to 6 mg/l; for a 10 kg child consuming 1 litre/day, the value would be up to 2 mg/l. However, the dietary bromide contribution for a 10 kg child would probably be less than that for an adult. These are reasonably conservative values, and they are unlikely to be encountered in drinking-water supplies.

Bromide can be involved in the reaction between chlorine and naturally occurring organic matter in drinking-water, forming brominated and mixed chloro-bromo by-products, such as trihalomethanes (THMs) and halogenated acetic acids (HAAs), or it can react with ozone to form bromate. The levels of bromide that can result in the formation of these substances are well below the health-based values suggested above. This guidance applies specifically to inorganic bromide ion and not to bromate or organohalogen compounds, for which individual health-based guideline values have been developed.

### ***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 as a result of either saltwater intrusion resulting from drought conditions or pollution. Brominated acetates are generally present in surface water and groundwater distribution systems at mean concentrations below 5 µg/l.

Reason for not establishing guideline values	Available data inadequate to permit derivation of health-based guideline values
Assessment date	2003
Principal references	IPCS (2000) <i>Disinfectants and disinfectant by-products</i> WHO (2003) <i>Brominated acetic acids in drinking-water</i>

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. 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.

## 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/l (3 µg/l)
Occurrence	Levels in drinking-water usually less than 1 µg/l
PTMI	25 µg/kg body weight, based on the relationship between $\beta_2$ -microglobulin excretion in urine and cadmium excretion in urine for individuals who are 50 years of age and older
Limit of detection	0.01 µg/l by ICP-MS; 2 µg/l by flame AAS
Treatment performance	0.002 mg/l should be achievable using coagulation or precipitation softening
Guideline value derivation	
• allocation to water	10% of provisional tolerable monthly intake (PTMI) because of high intake from food
• weight	60 kg adult
• consumption	2 litres/day
Additional comments	Although new information indicates that a proportion of the general population may be at increased risk for tubular dysfunction when exposed at the current PTMI, the risk estimates that can be made at present are imprecise.  It is recognized that the margin between the PTMI and the actual monthly intake of cadmium by the general population is small and that this margin may be even smaller in smokers.
Assessment date	2011
Principal references	FAO/WHO (2011) <i>Evaluation of certain food additives and contaminants</i> WHO (2011) <i>Cadmium in drinking-water</i>

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 (probably carcinogenic to humans). 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.

In its recent evaluation of cadmium, JECFA found that data relating excretion of the biomarker  $\beta_2$ -microglobulin in urine to cadmium excretion in urine for individuals who are 50 years of age and older provided the most reliable basis on which to determine a critical concentration of cadmium in the urine. Urinary excretion of less

than 5.24 µg of cadmium per gram creatinine was not associated with an increased excretion of β<sub>2</sub>-microglobulin, and the dietary exposure that would result in a urinary cadmium concentration at the breakpoint of 5.24 µg/g creatinine was estimated to be 0.8 µg/kg body weight per day or about 25 µg/kg body weight per month. Because of cadmium's exceptionally long half-life, the previous PTWI of 7 µg/kg body weight was withdrawn, and a PTMI of 25 µg/kg body weight was established.

### **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.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2006
Principal references	FAO/WHO (2002) <i>Pesticide residues in food—2001 evaluations</i> WHO (2008) <i>Carbaryl in drinking-water</i>

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 body weight. This was based on a lowest-observed-adverse-effect level (LOAEL) of 15 mg/kg body weight per day and application of a safety factor of 2000 (10 for interspecies variation, 10 for intraspecies variation and 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 µg/l (rounded value) can be determined from the JMPR ADI of 0–0.008 mg/kg body weight, assuming a 60 kg adult drinking 2 litres of water per day and allowing 20% of the upper limit 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.

### **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 physicochemical 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.

## 12. CHEMICAL FACT SHEETS

Guideline value	0.007 mg/l (7 µg/l)
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/l) measured in groundwater
ADI	0–0.002 mg/kg body weight based on a NOAEL of 0.22 mg/kg 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/l by GC with a nitrogen–phosphorus detector; 0.9 µg/l by reversed-phase HPLC with a fluorescence detector
Treatment performance	1 µg/l should be achievable using GAC
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 10% of upper limit of ADI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
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.
Assessment date	1998
Principal references	FAO/WHO (1997) <i>Pesticide residues in food—1996 evaluations</i> WHO (2003) <i>Carbofuran in drinking-water</i>

Carbofuran is highly toxic after acute oral administration. The main systemic effect of carbofuran poisoning in short-term 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.

### **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/l (4 µg/l)
Occurrence	Concentrations in drinking-water generally less than 5 µg/l

TDI	1.4 µg/kg body weight, based on a NOAEL of 1 mg/kg body weight per day for hepatotoxic effects in a 12-week oral gavage study in rats, adjusting for daily dosing and applying an uncertainty factor of 500 (100 for interspecies 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/l by GC-ECD or GC-MS
Treatment performance	0.001 mg/l should be achievable using air stripping
Guideline value 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 <sup>-4</sup> , 10 <sup>-5</sup> and 10 <sup>-6</sup> calculated by linear extrapolation.
Assessment date	2003
Principal references	IPCS (1999) <i>Carbon tetrachloride</i> WHO (2003) <i>Carbon tetrachloride in drinking-water</i>

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.

### **Chloral hydrate**

Chloral hydrate, or trichloroacetaldehyde, 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/l, but concentrations are usually below 10 µg/l. Concentrations are generally higher in surface water than in groundwater, and concentrations appear to increase during distribution.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2004
Principal references	IPCS (2000) <i>Chloral hydrate</i> IPCS (2000) <i>Disinfectants and disinfectant by-products</i> WHO (2005) <i>Chloral hydrate in drinking-water</i>



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 for the genotoxicity of chloral hydrate.

A health-based value of 0.1 mg/l (rounded figure) can be calculated on the basis of a TDI of 0.0045 mg/kg body weight derived based on an increased incidence of liver histopathology observed in 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 of health concern, 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.

### ***Chloramines (monochloramine, dichloramine, trichloramine)***

Monochloramine, dichloramine and trichloramine are considered by-products of drinking-water chlorination, being formed when chlorine and ammonia are added to water. Monochloramine may also be added to maintain residual disinfection activity in potable water distribution systems. Because higher chloramines are formed only occasionally and cause taste and odour problems at concentrations lower than those at which monochloramine causes taste and odour problems, only monochloramine has been considered for development of a health-based guideline value. Chloramine is rapidly decomposed in the stomach by gastric juice. 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 haloketones, chloropicrin, cyanogen chloride, HAAs, haloacetonitriles, aldehydes and chlorophenols, has been reported. Monochloramine, the most abundant chloramine, is recognized as a less effective disinfectant than chlorine and is used as a secondary disinfectant to maintain a residual in distribution systems.

Guideline value	<i>Monochloramine</i> : 3 mg/l (3000 µg/l)
Occurrence	Typical chloramine concentrations of 0.5–2 mg/l 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 body weight, based on a NOAEL of 9.4 mg/kg body weight per day, the highest dose administered to male rats in a 2-year United States National Toxicology Program (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/l by colorimetric methods
Treatment performance	It is possible to reduce the concentration of chloramine effectively to zero (< 0.1 mg/l) 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 value derivation	
• allocation to water	100% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Additional comments	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/l, and some at levels as low as 0.3 mg/l.
Assessment date	2003
Principal references	IPCS (2000) <i>Disinfectants and disinfectant by-products</i> WHO (2003) <i>Monochloramine in drinking-water</i>
Reason for not establishing guideline values	Available data inadequate to permit derivation of health-based guideline values for <i>dichloramine</i> and <i>trichloramine</i>
Assessment date	1993
Principal references	IPCS (2000) <i>Disinfectants and disinfectant by-products</i>

### Monochloramine

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 (not classifiable as to its carcinogenicity to humans). In the NTP bioassay in two species, the incidence of mononuclear cell leukaemias in female rats was increased, but no other increases in tumour incidence were observed. IPCS did not consider the increase in mononuclear cell leukaemia to be treatment related.

### Dichloramine and trichloramine

Dichloramine and trichloramine have not been extensively studied, and available data are inadequate to permit derivation of health-based guideline values for either of these chemicals. However, these substances can cause taste and odour problems (see chapter 10) if formation of monochloramine is not controlled adequately.

**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, highly immobile in soil and 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/l (0.2 µg/l)
Occurrence	Has been detected in both drinking-water and groundwater, usually at levels below 0.1 µg/l
PTDI	0.5 µg/kg body weight based on a NOAEL of 50 µg/kg 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 (10 each for interspecies and intraspecies variation)
Limit of detection	0.014 µg/l by GC with ECD
Treatment performance	0.1 µg/l should be achievable using GAC
Guideline value 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.
Assessment date	2003
Principal references	FAO/WHO (1995) <i>Pesticide residues in food—1994 evaluations</i> WHO (2003) <i>Chlordane in drinking-water</i>

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.

**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.

Reason for not establishing a guideline value	Not of health concern at levels found in drinking-water
Additional comments	May affect acceptability of drinking-water
Assessment date	1993
Principal reference	WHO (2003) <i>Chloride in drinking-water</i>

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/l can give rise to detectable taste in water (see chapter 10).

### 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. Concentrations of chlorate and some perchlorates increase in hypochlorite solutions upon storage at high ambient temperatures or when new hypochlorite is added to old hypochlorite.

Guideline value	5 mg/l (5000 µg/l)
Occurrence	Present in most disinfected drinking-water at concentrations of 0.2–1 mg/l
TDI	150 µg/kg 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/l following pre-column derivatization to 4-bromoacetanilide by HPLC; 10 µg/l as free chlorine by colorimetry; 200 µg/l by ion chromatography
Treatment performance	It is possible to reduce the concentration of chlorine effectively to zero (< 0.1 mg/l) 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 value derivation	<ul style="list-style-type: none"> <li>● allocation to water 100% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
Additional comments	<p>The guideline value is conservative, as no adverse effect level was identified in the critical study.</p> <p>Most individuals are able to taste chlorine at the guideline value.</p>

## 12. CHEMICAL FACT SHEETS

Assessment date	1993
Principal reference	WHO (2003) <i>Chlorine in drinking-water</i>

In humans and experimental animals exposed to chlorine in drinking-water, no specific adverse treatment-related effects have been observed. IARC has classified hypochlorite in Group 3 (not classifiable as to its carcinogenicity to humans).

### **Chlorite and chlorate**

Chlorite and chlorate are disinfection by-products resulting from the use of chlorine dioxide as a disinfectant and for odour and 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. Chlorate is also formed in sodium hypochlorite solution that is stored for long periods, particularly at high ambient temperatures.

Provisional guideline values	<i>Chlorite</i> : 0.7 mg/l (700 µg/l) <i>Chlorate</i> : 0.7 mg/l (700 µg/l)
	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/l; however, the combined levels will not exceed the dose of chlorine dioxide applied. Chlorate can also form in hypochlorite solutions on storage.
TDIs	<i>Chlorite</i> : 30 µg/kg body weight based on a NOAEL of 2.9 mg/kg body weight per day identified in a two-generation study in rats, based on lower startle amplitude, decreased absolute brain weights in two generations and altered liver weights in two generations, using an uncertainty factor of 100 (10 each for interspecies and intraspecies variation) <i>Chlorate</i> : 30 µg/kg body weight based on a NOAEL of 30 mg/kg body weight per day in a 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 interspecies and intraspecies variation and 10 for the short duration of the study)
Limit of detection	5 µg/l by ion chromatography with suppressed conductivity detection for chlorate

Treatment performance	It is possible to reduce the concentration of chlorine dioxide effectively to zero (< 0.1 mg/l) 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/l, although concentrations above 1 mg/l 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 less than 0.2 mg/l. 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 value derivation	<ul style="list-style-type: none"> <li>• allocation to water 80% of TDI</li> <li>• weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>
Assessment date	2003
Principal references	IPCS (2000) <i>Disinfectants and disinfectant by-products</i> WHO (2005) <i>Chlorite and chlorate in drinking-water</i>

## 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 provisional guideline value for chlorite is adequately protective for potential toxicity from chlorine dioxide. The taste and odour threshold for this compound is 0.4 mg/l.

## 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 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 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 well-conducted 90-day study in rats is available. High doses of chlorate can also interfere with thyroid function.

**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/l and usually less than 1 µg/l.

Reason for not establishing guideline values	Available data inadequate to permit derivation of health-based guideline values for any of the chloroacetones
Assessment date	1993
Principal reference	WHO (2003) <i>Chloroacetones in drinking-water</i>

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 setting of guideline values for 1,1-dichloroacetone or any of the other chloroacetones.

**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	<i>2,4,6-Trichlorophenol</i> : 0.2 mg/l (200 µg/l)
Occurrence	Concentrations of chlorophenols in drinking-water usually less than 1 µg/l
Basis of guideline value 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/l by formation of pentafluorobenzyl ether derivatives; 0.01 µg/l using GC with ECD
Treatment performance	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.
Assessment date	1993
Principal reference	WHO (2003) <i>Chlorophenols in drinking-water</i>

Reason for not establishing guideline values	Available data inadequate to permit derivation of health-based guideline values for <i>2-chlorophenol</i> and <i>2,4-dichlorophenol</i>
Assessment date	1993
Principal reference	WHO (2003) <i>Chlorophenols in drinking-water</i>

**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 (possibly carcinogenic to humans).

**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/l.

Reason for not establishing a guideline value	Available data inadequate to permit derivation of health-based guideline value
Assessment date	1993
Principal reference	WHO (2003) <i>Chloropicrin in drinking-water</i>

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.

**Chlorotoluron**

Chlorotoluron (CAS No. 15545-48-9) is a pre-emergence 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/l (30 µg/l)
Occurrence	Detected in drinking-water at concentrations of less than 1 µg/l
TDI	11.3 µg/kg body weight, derived from a NOAEL of 11.3 mg/kg body weight per day for systemic effects in a 2-year feeding study in mice using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for evidence of carcinogenicity)



## 12. CHEMICAL FACT SHEETS

Limit of detection	0.1 µg/l by separation by reversed-phase HPLC followed by UV and electrochemical detection
Treatment performance	0.1 µg/l should be achievable using GAC
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 10% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
Assessment date	1993
Principal reference	WHO (2003) <i>Chlorotoluron in drinking-water</i>

Chlorotoluron is of low toxicity following single, short-term and long-term exposures in experimental 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.

### **Chlorpyrifos**

Chlorpyrifos (CAS No. 2921-88-2) is a broad-spectrum organophosphorus insecticide used for the control of mosquitoes, 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 the WHO Pesticide Evaluation Scheme (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 phases into organic phases in the environment.

Guideline value	0.03 mg/l (30 µg/l)
Occurrence	Detected in surface waters in the USA, usually at concentrations below 0.1 µg/l; also detected in groundwater in less than 1% of the wells tested, usually at concentrations below 0.01 µg/l
ADI	0–0.01 mg/kg body weight on the basis of a NOAEL of 1 mg/kg 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 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/l by GC using ECD or flame photometric detection
Treatment performance	No data available; should be amenable to treatment by coagulation (10–20% removal), activated carbon adsorption and ozonation
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 10% of upper limit of ADI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>

Assessment date	2003
Principal references	FAO/WHO (2000) <i>Pesticide residues in food—1999 evaluations</i> WHO (2003) <i>Chlorpyrifos in drinking-water</i>

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.

### **Chromium**

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

Provisional guideline value	<i>Total chromium</i> : 0.05 mg/l (50 µg/l) The guideline value is designated as provisional because of uncertainties in the toxicological database.
Occurrence	Total chromium concentrations in drinking-water usually less than 2 µg/l, although concentrations as high as 120 µg/l 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/l for total chromium by AAS
Treatment performance	0.015 mg/l should be achievable using coagulation
Assessment date	1993
Principal reference	WHO (2003) <i>Chromium in drinking-water</i>

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 an NTP study has shown evidence for carcinogenicity via the oral route at high doses. However, there is evidence that the dose–response relationship at low doses is non-linear, because chromium(VI) is reduced to chromium(III) in the stomach and gastrointestinal tract. 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 (not classifiable as to its carcinogenicity to humans). Chromium(VI) compounds are active in a wide range of in vitro and in vivo genotoxicity tests, whereas chromium(III) compounds are not.

### **Copper**

Copper is both an essential nutrient and a drinking-water contaminant. It is used to make pipes, valves and fittings and is present in alloys and coatings. Copper sulfate

## 12. CHEMICAL FACT SHEETS

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 above 1 mg/l). 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/l (2000 µg/l)
Occurrence	Concentrations in drinking-water range from ≤ 0.005 to > 30 mg/l, primarily as a result of the corrosion of interior copper plumbing
Basis of guideline value 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 µg/l by ICP-MS; 0.3 µg/l by ICP–optical emission spectroscopy; 0.5 µg/l by flame AAS
Treatment performance	Copper is not removed by conventional treatment processes. However, copper is not normally a raw water contaminant.
Additional comments	<p>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.</p> <p>Staining of laundry and sanitary ware occurs at copper concentrations above 1 mg/l. At levels above 2.5 mg/l, copper imparts an undesirable bitter taste to water; at higher levels, the colour of water is also impacted.</p> <p>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.</p>
Assessment date	2003
Principal references	<p>IPCS (1998) <i>Copper</i></p> <p>WHO (2003) <i>Copper in drinking-water</i></p>

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 mg/day), 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 experimental animals were not considered helpful in establishing the upper limit of the acceptable range of oral intake owing 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, as 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-hour 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.

### **Cyanazine**

Cyanazine (CAS No. 21725-46-2) is a member of the triazine family of herbicides. It is used as a pre-emergence 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/l (0.6 µg/l)
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/l have been measured in surface water and groundwater, respectively
TDI	0.198 µg/kg body weight based on a NOAEL of 0.198 mg/kg body weight for hyperactivity in male rats in a 2-year toxicity/carcinogenicity study, using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for limited evidence of carcinogenicity)
Limit of detection	0.01 µg/l by GC-MS
Treatment performance	0.1 µg/l should be achievable using GAC
Guideline value derivation	<ul style="list-style-type: none"> <li>• allocation to water 10% of TDI</li> <li>• weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>
Assessment date	1998
Principal reference	WHO (2003) <i>Cyanazine in drinking-water</i>

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

### **Cyanide**

Cyanides can be found in some foods, particularly in some developing countries, and they are occasionally found in drinking-water, but usually only at very low concentrations. However, there are occasions on which large spills of cyanide, associated with industry, occur, and these can give rise to very high concentrations in drinking-water source waters, particularly surface waters.

## 12. CHEMICAL FACT SHEETS

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern, except in emergency situations following a spill to a water source
Assessment date	2009
Principal references	IPCS (2004) <i>Hydrogen cyanide and cyanides</i> WHO (2009) <i>Cyanide in drinking-water</i>

Cyanide is highly acutely toxic. It is detoxified in the liver by first-pass metabolism following oral exposure. As a consequence, exposure to a dose spread over a longer period, through a day, for example, will result in lower toxicity, or higher tolerance, than the same dose given in a single bolus dose. Exposure to high doses can give rise to thyroid toxicity as a secondary effect of exposure due to the inhibition of iodine uptake from the thiocyanate generated through the detoxifying action of rhodanese. It is difficult to interpret human data in view of the difficulty in assessing the actual absorbed dose in humans following acute fatal intoxication and the lack of well-conducted studies on sublethal toxicity.

There is a need for guidance regarding concentrations that would not be of concern for public health following short-term exposure to cyanide. However, because cyanide is unlikely to occur in drinking-water at concentrations of health concern, it is considered unnecessary to derive a formal guideline value for short-term exposure to cyanide.

The data on acute exposure to cyanide are unsuitable for use in deriving a health-based value for short-term exposure because of the high uncertainty surrounding the data. Using the NOAEL for effects on the reproductive organs of male rats in a 13-week study and an uncertainty factor of 100, a TDI of 0.045 mg/kg body weight can be derived. Because this health-based value is intended for short-term use and exposure would not exceed 5 days, it is considered to be acceptable to allocate 40% of the TDI to drinking-water to allow for exposure to cyanogenic glycosides in food. Therefore, assuming a 60 kg adult drinking 2 litres of water per day with an allocation of 40% of the TDI to drinking-water, a health-based value of 0.5 mg/l (rounded value) for short-term exposure can be calculated.

This health-based value is well below the level that is normally considered to be of health concern for humans. Cyanide is rapidly detoxified, and exposure spread throughout the day will further reduce the potential for effects. This health-based value would be suitable for use for a limited period of up to 5 days, which is the longest period likely to be required under the circumstances of such an emergency. However, it is probable that, in most circumstances, this value will be highly conservative for short-term exposure.

It should be noted that the lowest reported odour threshold for cyanide in drinking-water is 0.17 mg/l, which is below the short-term health-based value. It is therefore possible that a small number of individuals will detect cyanide by odour at concentrations below the health-based value.

The health-based value relates to total cyanide concentration at the tap, including cyanide from cyanogen chloride in drinking-water as a by-product of disinfection with chlorine. Cyanogen chloride rapidly breaks down to cyanide in the distribution system or when ingested. As the low levels of cyanide normally found in drinking-water

are mostly a consequence of the presence of cyanogen chloride, it is not considered necessary to develop a guideline value for long-term exposure to cyanide.

### **Cyanobacterial toxins: Microcystin-LR**

Among the cyanobacterial toxins, microcystins are the best-researched group and probably occur most frequently in fresh waters. Many practical considerations for the abatement of microcystins apply similarly to the other cyanotoxins (i.e. cylindrospermopsins, saxitoxins, anatoxin-a and anatoxin-a(s)), with one key difference that is relevant to the efficacy of their removal in drinking-water treatment: microcystins are usually cell-bound, and substantial amounts are released to the surrounding water only in situations of cell rupture (i.e. lysis), whereas the other cyanotoxins may occur to a larger extent dissolved in water.

Although microcystins may occur in fish, molluscs and shellfish from water bodies with cyanobacterial proliferation, human exposure to microcystins is largely through drinking-water or recreational use of water bodies with cyanobacterial blooms.

Among the more than 80 microcystins identified to date, only a few occur frequently and in high concentrations. Microcystin-LR is among the most frequently occurring and most toxic microcystin congeners. It is the only one for which enough toxicological data are available with which to derive a provisional guideline value. Frequently occurring cyanobacterial genera that may contain microcystins are *Microcystis*, *Planktothrix* and *Anabaena* (see also section 11.5).

Provisional guideline value	<i>Total microcystin-LR (free plus cell-bound): 0.001 mg/l (1 µg/l)</i>
	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 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/l 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/l by commercially available immunoassay kits (enzyme-linked immunosorbent assay) 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/l 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

## 12. CHEMICAL FACT SHEETS

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 value derivation	<ul style="list-style-type: none"> <li>● allocation to water      80% of TDI</li> <li>● weight                      60 kg adult</li> <li>● consumption              2 litres/day</li> </ul>
Assessment date	2003
Principal references	Chorus & Bartram (1999) <i>Toxic cyanobacteria in water</i> WHO (2003) <i>Cyanobacterial toxins: Microcystin-LR in drinking-water</i>

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 value 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. In 2006, IARC classified microcystin-LR as a possible carcinogen (Group 2B).

### Practical considerations

Cyanobacteria occur widely in lakes, reservoirs, ponds and slow-flowing rivers. Where their excessive growth leads to high cell numbers, sometimes termed “bloom” events, their toxins can reach concentrations in raw water that are potentially hazardous to human health. Blooms occur if concentrations of nutrients (phosphorus and nitrogen) are elevated, particularly in stagnant or very slowly flowing water bodies. Blooms tend to recur in the same water bodies. Cells of some cyanobacterial species may accumulate at the surface as scums or at the thermocline of thermally stratified reservoirs. Such accumulations may develop rapidly, and they may be of very variable duration (hours to weeks). In many circumstances, blooms and accumulations are seasonal.

A variety of resource protection and source management actions are available to decrease the probability of bloom occurrence. Among these, the most sustainable and effective measure is to reduce nutrient (particularly phosphorus) concentrations in the water body to levels sufficiently low to substantially limit the amount of cyanobacterial biomass that can grow. This is achieved by controlling nutrient loads from sewage effluents and from land areas. The latter involves controlling erosion as well as the amount of manure and fertilizers spread in the catchment. Further, hydrological management actions such as water body mixing and flushing can render hydrophysical conditions less suitable for cyanobacteria and thus shift plankton species from cyanobacteria to others (i.e. planktonic algae such as diatoms) that are less relevant to human health.

As microcystins almost always occur largely cell-bound, any drinking-water treatment that removes particles—i.e. soil or riverbank filtration, flocculation and filtration or dissolved air filtration—controls them effectively if the process is optimized to target their removal. This also applies to the cell-bound fraction of other cyanotoxins. Process operation should avoid cell rupture and toxin release. Hazardously high concentrations of dissolved cyanotoxins appear to occur less frequently. They are well removed by most types of activated carbon. Chlorination and ozonation are effective for the removal of many cyanotoxins at sufficiently high doses and contact times, but not very effective for saxitoxins. Potassium permanganate is effective for microcystins, whereas limited or no data are available at present for other toxins. Chlorine dioxide and chloramine are ineffective for removing cyanotoxins.

Cyanotoxin monitoring is most effectively based on surveillance of source water for evidence of cyanobacterial blooms or bloom-forming potential (i.e. nutrient levels and phytoplankton species composition), with vigilance increased where such events occur. In contrast, monitoring finished water against target cyanotoxin concentrations is unsatisfactory for determining whether or not it is safe, because of the large variety of toxins (particularly of microcystins), the lack of guideline values for all but one (i.e. microcystin-LR) against which to monitor and the lack of analytical standards for many. Analysis of cyanotoxins is particularly useful for validating and optimizing the efficacy of control measures such as riverbank filtration or treatment. A caveat in cyanotoxin analysis is the need for extraction of the cell-bound fraction from the cells; although this is easy to do, particularly for microcystins, neglecting extraction from cells will lead to dramatic underestimation of concentrations.

### **Cyanogen chloride**

Cyanogen chloride may be formed as a by-product of chloramination or chlorination of water. It is also formed by the chlorination of cyanide ion present in raw water.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2009
Principal references	IPCS (2004) <i>Hydrogen cyanide and cyanides</i> WHO (2009) <i>Cyanogen chloride in drinking-water</i>

Cyanogen chloride is rapidly metabolized to cyanide in the body. There are few data available on the oral toxicity of cyanogen chloride.

As cyanogen chloride is unlikely to be found in drinking-water at concentrations that are of health concern, it is considered unnecessary to develop a formal guideline value for cyanogen chloride. Instead, for guidance purposes, a health-based value is derived based on cyanide.

Using a NOAEL for cyanide of 4.5 mg/kg body weight per day for minor changes in the testis in a subchronic study in which rats were exposed through their drinking-water and an uncertainty factor of 100, a TDI for cyanide of 0.045 mg/kg body weight (corresponding to a cyanogen chloride dose of 0.11 mg/kg body weight) can be



derived. In view of the minor nature of the changes observed and the NOAEL in a previous chronic study, it is not considered necessary to include an additional uncertainty factor to allow for the length of the study. Further, it appears that a dose that may be toxic in acute poisoning would certainly be tolerated under chronic conditions, owing to efficient detoxification. Assuming a 60 kg adult drinking 2 litres of water per day and allowing 20% of the TDI to come from water because of the potential for exposure to cyanogenic glycosides in food, the health-based value for long-term exposure is 0.3 mg/l for cyanide or 0.6 mg/l for cyanogen chloride (rounded values).

Although low concentrations of cyanide in raw waters will be converted to cyanogen chloride by chlorination, cyanogen chloride may also be formed during the production of chloramines in situ as a residual disinfectant to maintain the hygienic condition of the distribution system. It is important that treatment be optimized to minimize the formation of cyanogen chloride while maintaining adequate chloramine residuals where chloramination is practised.

### 2,4-D

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/l (30 µg/l)
Occurrence	Levels in water usually below 0.5 µg/l, although concentrations as high as 30 µg/l have been measured
ADI	0–0.01 mg/kg 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 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/l by gas–liquid chromatography with electrolytic conductivity detection
Treatment performance	1 µg/l should be achievable using GAC
Guideline value derivation	
• allocation to water	10% of upper limit 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.
Assessment date	1998
Principal references	FAO/WHO (1997) <i>Pesticide residues in food—1996 evaluations</i> WHO (2003) <i>2,4-D in drinking-water</i>

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 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.

### **2,4-DB**

The half-lives for degradation of chlorophenoxy herbicides, including 2,4-DB, or 2,4-dichlorophenoxybutyric acid (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/l (90 µg/l)
Occurrence	Chlorophenoxy herbicides not frequently found in drinking-water; when detected, concentrations usually no greater than a few micrograms per litre
TDI	30 µg/kg body weight, based on a NOAEL of 3 mg/kg 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 interspecies and intraspecies variation)
Limit of detection	1 µg/l to 1 mg/l 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 performance	0.1 µg/l should be achievable using GAC
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 10% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
Additional comments	The NOAEL used in the guideline value derivation is similar to the NOAEL of 2.5 mg/kg body weight per day obtained in a short-term study in dogs and the NOAEL for hepatocyte hypertrophy of 5 mg/kg body weight per day obtained in a 3-month study in rats.
Assessment date	1993
Principal reference	WHO (2003) <i>Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in drinking-water</i>

Chlorophenoxy herbicides, as a group, have been classified in Group 2B (possibly carcinogenic to humans) by IARC. However, the available data from studies in exposed populations and experimental 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.

### **DDT and metabolites**

The structure of dichlorodiphenyltrichloroethane, or DDT (CAS No. 107917-42-0), permits several different isomeric forms; 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, although exposure has significantly decreased as a consequence of the greatly reduced use of DDT for all except specialist applications.

Guideline value	0.001 mg/l (1 µg/l)
Occurrence	Detected in surface water at concentrations below 1 µg/l; also detected in drinking-water at 100-fold lower concentrations
PTDI	0.01 mg/kg body weight based on a NOAEL of 1 mg/kg body weight per day for developmental toxicity in rats, applying an uncertainty factor of 100 (for interspecies and intraspecies variation)
Limit of detection	0.011 µg/l by GC using ECD
Treatment performance	0.1 µg/l should be achievable using coagulation or GAC
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 1% of PTDI</li> <li>● weight 10 kg child</li> <li>● consumption 1 litre/day</li> </ul>
Additional comments	<p>DDT is listed under the Stockholm Convention on Persistent Organic Pollutants. Hence, monitoring may occur in addition to that required by drinking-water guidelines.</p> <p>It should be noted that the level of DDT and its metabolites in food has been falling steadily, and the allocation of 1% of the PTDI may be very conservative.</p> <p>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.</p> <p>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.</p>

Assessment date	2003
Principal references	FAO/WHO (2001) <i>Pesticide residues in food—2000 evaluations</i> WHO (2003) <i>DDT and its derivatives in drinking-water</i>

A working group convened by IARC classified the DDT complex (the mixture of the various isomers of DDT and associated compounds) 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 United States Agency for Toxic Substances and Disease Registry concluded that the DDT complex could impair reproduction and 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 high doses of DDT.

### **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 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.

Reason for not establishing a guideline value	Available data inadequate to permit derivation of health-based guideline values for any of the dialkyltins
Assessment date	2003
Principal reference	WHO (2003) <i>Dialkyltins in drinking-water</i>

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.

### **1,2-Dibromo-3-chloropropane**

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

## 12. CHEMICAL FACT SHEETS

Guideline value	0.001 mg/l (1 µg/l)
Occurrence	Limited survey found levels of up to a few micrograms per litre in drinking-water
Basis of guideline value 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/l by GC with ECD
Treatment performance	1 µg/l should be achievable using air stripping followed by GAC
Additional comments	The guideline value of 1 µg/l should be protective for the reproductive toxicity of DBCP.
Assessment date	1993
Principal reference	WHO (2003) <i>1,2-Dibromo-3-chloropropane in drinking-water</i>

On the basis of 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.

### **1,2-Dibromoethane**

1,2-Dibromoethane (CAS No. 106-93-4), or ethylene dibromide, is used as a lead scavenger in tetraalkyl 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/l (0.4 µg/l)
	The guideline value is provisional owing 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/l
Basis of guideline value 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 mice exposed by gavage
Limit of detection	0.01 µg/l by microextraction GC-MS; 0.03 µg/l by purge-and-trap GC with halogen-specific detector; 0.8 µg/l by purge-and-trap capillary column GC with photoionization and electrolytic conductivity detectors in series

Treatment performance	0.1 µg/l should be achievable using GAC
Assessment date	2003
Principal references	IPCS (1995) <i>Report of the 1994 meeting of the Core Assessment Group</i> IPCS (1996) <i>1,2-Dibromoethane</i> WHO (2003) <i>1,2-Dibromoethane in drinking-water</i>

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 (probably carcinogenic to humans).

### **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/l (50 µg/l) The guideline value is designated as provisional on the basis of technical achievability.
Occurrence	Found in groundwater and surface water distribution systems at concentrations up to about 100 µg/l, with mean concentrations below 20 µg/l
Basis of guideline value derivation	Linear multistage model applied to combined data for carcinomas and adenomas in male mice exposed to doses up to 429 mg/kg body weight per day for up to 2 years
Limit of detection	< 0.1–0.4 µg/l by GC with ECD; practical quantification limit 1 µg/l
Treatment performance	Concentrations may be reduced by installing or optimizing coagulation to remove precursors or by controlling the pH during chlorination.
Additional comments	The concentration associated with a 10 <sup>-5</sup> upper-bound excess lifetime cancer risk is 40 µg/l. In some circumstances, however, it may not be possible to adequately disinfect potable water and maintain DCA levels below 40 µg/l, so the provisional guideline value of 50 µg/l is retained.

Assessment date	2004
Principal reference	WHO (2005) <i>Dichloroacetic acid in drinking-water</i>

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, as altered hepatic foci from treated mice were found to have three different types of cellular characteristics.

### ***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	<i>1,2-Dichlorobenzene</i> : 1 mg/l (1000 µg/l) <i>1,4-Dichlorobenzene</i> : 0.3 mg/l (300 µg/l)
Occurrence	Have been found in raw water sources at levels as high as 10 µg/l and in drinking-water at concentrations up to 3 µg/l; much higher concentrations (up to 7 mg/l) present in contaminated groundwater
TDIs	<i>1,2-Dichlorobenzene</i> : 429 µg/kg body weight, based on a NOAEL of 60 mg/kg body weight per day for tubular degeneration of the kidney identified in a 2-year mouse gavage study, adjusting for daily dosing and using an uncertainty factor of 100 (for interspecies and intraspecies variation) <i>1,4-Dichlorobenzene</i> : 107 µg/kg body weight, based on a LOAEL of 150 mg/kg body weight per day for kidney effects identified in a 2-year rat study, adjusting for daily dosing and using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for the use of a LOAEL instead of a NOAEL and the carcinogenicity end-point)
Limit of detection	0.01–0.25 µg/l by gas–liquid chromatography with ECD; 3.5 µg/l by GC using a photoionization detector
Treatment performance	0.01 mg/l should be achievable using air stripping
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 10% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>

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/l, respectively.
Assessment date	1993
Principal reference	WHO (2003) <i>Dichlorobenzenes in drinking-water</i>

Reason for not establishing a guideline value	Available data inadequate to permit derivation of health-based guideline value for <i>1,3-dichlorobenzene</i>
Assessment date	1993
Principal reference	WHO (2003) <i>Dichlorobenzenes in drinking-water</i>

### 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 (possibly carcinogenic to humans). 1,4-DCB is not considered to be genotoxic, and the relevance for humans of the tumours observed in experimental animals is doubtful.

### **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/l in drinking-water. It is primarily of concern for groundwater.

Reason for not establishing a guideline value	Available data inadequate to permit derivation of health-based guideline value
Assessment date	1993
Principal reference	WHO (2003) <i>1,1-Dichloroethane in drinking-water</i>

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-term 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.

### **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 was used as a scavenger for tetraethyl lead in gasoline. 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	0.03 mg/l (30 µg/l)
Occurrence	Has been found in drinking-water at levels of up to a few micrograms per litre
Basis of guideline value derivation	Applying the linearized multistage model to haemangiosarcomas observed in male rats in a 78-week gavage study
Limit of detection	0.03 µg/l by GC with photoionization detection; 0.03–0.2 µg/l by GC with electrolytic conductivity detector; 0.06–2.8 µg/l by GC-MS; 5 µg/l by GC with flame ionization detection (FID)
Treatment performance	0.0001 mg/l should be achievable using GAC
Additional comments	The guideline value of 0.03 mg/l is consistent with the value derived from IPCS (1998), based on a 10 <sup>-5</sup> risk level.
Assessment date	2003
Principal references	IPCS (1995) <i>1,2-Dichloroethane</i> , 2nd ed. IPCS (1998) <i>1,2-Dichloroethane</i> WHO (2003) <i>1,2-Dichloroethane in drinking-water</i>

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.

### **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/m<sup>3</sup> 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/l and in public drinking-water supplies at concentrations up to 0.5 µg/l.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2004
Principal references	IPCS (2003) <i>1,1-Dichloroethene (vinylidene chloride)</i> WHO (2005) <i>1,1-Dichloroethene in drinking-water</i>

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 (not classifiable as to its carcinogenicity to humans). 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/l (rounded value) can be calculated on the basis of a TDI of 0.046 mg/kg body weight, derived using the benchmark dose (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.

### **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 other 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/l (50 µg/l)
Occurrence	Has been found in drinking-water supplies derived from groundwater at levels up to 120 µg/l
TDI	17 µg/kg body weight, based on a NOAEL (for increases in serum alkaline phosphatase levels and increased thymus weight) of 17 mg/kg 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 interspecies and intraspecies variation and 10 for the short duration of the study)
Limit of detection	0.17 µg/l by GC-MS

## 12. CHEMICAL FACT SHEETS

Treatment performance	0.01 mg/l should be achievable using GAC or air stripping
Guideline value derivation	<ul style="list-style-type: none"> <li>• allocation to water 10% of TDI</li> <li>• weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>
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.
Assessment date	1993
Principal reference	WHO (2003) <i>1,2-Dichloroethene in drinking-water</i>

There is little information on the absorption, distribution or excretion of 1,2-dichloroethene. However, by analogy with 1,1-dichloroethene, 1,2-dichloroethene 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.

### **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/l (20 µg/l)
Occurrence	Has been found in surface water samples at concentrations ranging from 0.1 to 743 µg/l; levels usually higher in groundwater because volatilization is restricted, with concentrations as high as 3600 µg/l reported; mean concentrations in drinking-water less than 1 µg/l
TDI	6 µg/kg body weight, derived from a NOAEL of 6 mg/kg body weight per day for hepatotoxic effects in a 2-year drinking-water study in rats, using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for concern about carcinogenic potential)
Limit of detection	0.3 µg/l by purge-and-trap GC with MS detection (note that dichloromethane vapour readily penetrates tubing during the procedure)

Treatment performance	20 µg/l should be achievable using air stripping
Guideline value derivation	<ul style="list-style-type: none"> <li>• allocation to water 10% of TDI</li> <li>• weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>
Assessment date	1993
Principal reference	WHO (2003) <i>Dichloromethane in drinking-water</i>

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 (possible human carcinogen); 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.

### **1,2-Dichloropropane**

1,2-Dichloropropane (CAS No. 78-87-5), or 1,2-DCP, 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 tetrachloroethene 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/l (40 µg/l)
	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/l, although levels as high as 440 µg/l have been measured in well water
TDI	14 µg/kg body weight based on a LOAEL of 71.4 mg/kg body weight per day (100 mg/kg body weight per day adjusted for daily dosing) for changes in haematological parameters in a 13-week study in male rats, with an uncertainty factor of 5000 (100 for interspecies and intraspecies variation, 10 for use of a LOAEL and 5 to reflect limitations of the database, including the limited data on in vivo genotoxicity and use of a subchronic study)
Limit of detection	0.02 µg/l by purge-and-trap GC with an electrolytic conductivity detector or GC-MS
Treatment performance	1 µg/l should be achievable using GAC
Guideline value derivation	<ul style="list-style-type: none"> <li>• allocation to water 10% of TDI</li> <li>• weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>
Assessment date	1998

Principal reference	WHO (2003) <i>1,2-Dichloropropane (1,2-DCP) in drinking-water</i>
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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.

### **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.

Reason for not establishing a guideline value	Available data inadequate to permit derivation of health-based guideline value
Assessment date	1993
Principal reference	WHO (2003) <i>1,3-Dichloropropane in drinking-water</i>

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.

### **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/l (20 µg/l)
Occurrence	Has been found in surface water and groundwater at concentrations of a few micrograms per litre
Basis of guideline value 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/l by purge-and-trap packed column GC using an electrolytic conductivity detector or microcoulometric detector for the <i>cis</i> and <i>trans</i> isomers, respectively

Treatment performance	No information found on removal from water
Assessment date	1993
Principal reference	WHO (2003) <i>1,3-Dichloropropene in drinking-water</i>

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).

### **Dichlorprop**

The half-lives for degradation of chlorophenoxy herbicides, including dichlorprop (CAS No. 120-36-5), or 2,4-DP, in the environment are in the order of several days. Chlorophenoxy herbicides are not often found in food.

Guideline value	0.1 mg/l (100 µg/l)
Occurrence	Chlorophenoxy herbicides not frequently found in drinking-water; when detected, concentrations usually no greater than a few micrograms per litre
TDI	36.4 µg/kg body weight, based on a NOAEL of 3.64 mg/kg body weight per day for renal toxicity in a 2-year dietary study in rats, applying an uncertainty factor of 100 (for intraspecies and interspecies variation)
Limit of detection	1 µg/l to 1 mg/l 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 performance	No information found on removal from water
Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	1993
Principal reference	WHO (2003) <i>Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in drinking-water</i>

Chlorophenoxy herbicides, as a group, have been classified in Group 2B (possible human carcinogen) by IARC. However, the available data from studies in exposed populations and experimental 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.

### ***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).

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal reference	WHO (2003) <i>Di(2-ethylhexyl)adipate in drinking-water</i>

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 (not classifiable as to its carcinogenicity to humans).

A health-based value of 80 µg/l can be calculated for DEHA on the basis of a TDI of 280 µg/kg 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 of health concern, it is not considered necessary to derive a formal guideline value.

### ***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/l (8 µg/l)
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 body weight, based on a NOAEL of 2.5 mg/kg body weight per day for peroxisomal proliferation in the liver in rats, using an uncertainty factor of 100 for interspecies and intraspecies variation
Limit of detection	0.1 µg/l by GC-MS

Treatment performance	No information found on removal from water
Guideline value 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.
Assessment date	1993
Principal reference	WHO (2003) <i>Di(2-ethylhexyl)phthalate in drinking-water</i>

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. JECFA 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.

### **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 hours 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 body weight has been estimated.

Guideline value	0.006 mg/l (6 µg/l)
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	0–0.002 mg/kg body weight based on an apparent NOAEL of 1.2 mg/kg body weight per day for reproductive performance in a study of reproductive toxicity in rats, applying an uncertainty factor of 500 (100 for interspecies and intraspecies variation, 5 to take into consideration concern regarding whether the NOAEL could be a LOAEL)



## 12. CHEMICAL FACT SHEETS

Assessment date	2003
Principal references	FAO/WHO (1997) <i>Pesticide residues in food—1996 evaluations</i> WHO (2003) <i>Dimethoate in drinking-water</i>

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 multi-generation study of reproductive toxicity in rats, the NOAEL appeared to be 1.2 mg/kg 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, as 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.

### **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/l (50 µg/l)
Occurrence	Has been measured in surface water at concentrations up to 40 µg/l and in groundwater at concentrations up to 80 µg/l
TDI	16 µg/kg body weight, based on a NOAEL of 16 mg/kg 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 interspecies and intraspecies variation and 10 for non-genotoxic carcinogenicity)
Guideline value derivation	
<ul style="list-style-type: none"> <li>● allocation to water</li> <li>● weight</li> <li>● consumption</li> </ul>	10% of TDI 60 kg adult 2 litres/day
Basis of guideline value 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/l by GC-MS
Treatment performance	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).
Assessment date	2004
Principal reference	WHO (2005) <i>1,4-Dioxane in drinking-water</i>

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 in Group 2B (possibly carcinogenic to humans).

### **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/l) 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.

Reason for not establishing a guideline value	May be used as an aquatic herbicide for the control of free-floating and submerged aquatic weeds in ponds, lakes and irrigation ditches, but rarely found in drinking-water
Assessment date	2003
Principal references	FAO/WHO (1994) <i>Pesticide residues in food—1993 evaluations</i> WHO (2003) <i>Diquat in drinking-water</i>

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/l for diquat ion can be calculated on the basis of an ADI of 0–0.002 mg of diquat ion per kilogram 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 formal guideline value. It should also be noted that the limit of detection of diquat in water is 1 µg/l, and its practical quantification limit is about 10 µg/l.

### **Edetic acid**

Human exposure to edetic acid, also known as ethylenediaminetetraacetic acid or EDTA, arises directly from its use in food additives, medicines and personal care and

## 12. CHEMICAL FACT SHEETS

hygiene products. Exposure to EDTA from drinking-water will be mostly very low 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	<i>EDTA (as the free acid): 0.6 mg/l (600 µg/l)</i>
Occurrence	Present in surface waters generally at concentrations below 70 µg/l, although higher concentrations (900 µg/l) have been measured; detected in drinking-water prepared from surface waters at concentrations of 10–30 µg/l
ADI	0–1.9 mg/kg body weight as the free acid (ADI of 0–2.5 mg/kg body weight proposed by JECFA for calcium disodium edetate as a food additive)
Limit of detection	1 µg/l by potentiometric stripping analysis
Treatment performance	0.01 mg/l using GAC plus ozonation
Guideline value derivation	
• allocation to water	1% of upper limit 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.
Assessment date	1998
Principal reference	WHO (2003) <i>Edetic acid (EDTA) in drinking-water</i>

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 experimental animals. The vast clinical experience of the use of EDTA in the treatment of metal poisoning has demonstrated its safety in humans.

### **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/l. 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.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	FAO/WHO (1999) <i>Pesticide residues in food—1998 evaluations</i> WHO (2003) <i>Endosulfan in drinking-water</i>

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/l can be calculated for endosulfan on the basis of an ADI of 0–0.006 mg/kg 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 of health concern, it is not considered necessary to derive a formal guideline value.

### **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. There is now very little use of endrin. Small amounts of endrin are present in some foods, but the total intake from food has decreased significantly.

Guideline value	0.0006 mg/l (0.6 µg/l)
Occurrence	Traces of endrin found in the drinking-water supplies of several countries
PTDI	0.2 µg/kg body weight, based on a NOAEL of 0.025 mg/kg body weight per day in a 2-year study in dogs and applying an uncertainty factor of 100 for interspecies and intraspecies variation
Limit of detection	0.002 µg/l by GC with ECD
Treatment performance	0.2 µg/l should be achievable using GAC
Guideline value derivation	
• allocation to water	10% of PTDI
• weight	60 kg adult
• consumption	2 litres/day

## 12. CHEMICAL FACT SHEETS

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.
Assessment date	2003
Principal references	FAO/WHO (1995) <i>Pesticide residues in food—1994 evaluations</i> IPCS (1992) <i>Endrin</i> WHO (2003) <i>Endrin in drinking-water</i>

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.

### **Epichlorohydrin**

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

Provisional guideline value	0.0004 mg/l (0.4 µg/l) 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 body weight, on the basis of a LOAEL of 2 mg/kg body weight per day for forestomach hyperplasia observed in a 2-year gavage study in rats, adjusting for daily dosing and using an uncertainty factor of 10 000 to take into consideration interspecies and intraspecies variation (100), the use of a LOAEL instead of a NOAEL (10) and carcinogenicity (10)
Limit of detection	0.01 µg/l by GC with ECD; 0.1 and 0.5 µg/l by GC-MS; 10 µg/l by GC with FID
Treatment performance	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 value derivation	<ul style="list-style-type: none"> <li>● allocation to water 10% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
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.
Assessment date	2003
Principal reference	WHO (2003) <i>Epichlorohydrin in drinking-water</i>

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).

### **Ethylbenzene**

The primary sources of ethylbenzene in the environment are the petroleum industry and the use of petroleum products. Because of its physicochemical properties, more than 96% of ethylbenzene in the environment can be expected to be present in air. Values of up to 26 µg/m<sup>3</sup> in air have been reported. Ethylbenzene is found in trace amounts in surface water, groundwater, drinking-water and food.

Guideline value	0.3 mg/l (300 µg/l)
Occurrence	Concentrations in drinking-water generally below 1 µg/l; levels up to 300 µg/l have been reported in groundwater contaminated by point emissions
TDI	97.1 µg/kg body weight, based on a NOAEL of 136 mg/kg body weight per day for hepatotoxicity and nephrotoxicity observed in a limited 6-month study in rats, adjusting for daily dosing and using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for the limited database and short duration of the study)
Limit of detection	0.002–0.005 µg/l by GC with photoionization detector; 0.03–0.06 µg/l by GC-MS
Treatment performance	0.001 mg/l should be achievable using air stripping
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 10% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
Additional comments	The guideline value exceeds the lowest reported odour threshold for ethylbenzene in drinking-water (0.002 mg/l).
Assessment date	1993
Principal reference	WHO (2003) <i>Ethylbenzene in drinking-water</i>

Ethylbenzene is readily absorbed by the oral, inhalation or dermal route. 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 vivo* systems.

### **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, mosquitoes and cockroaches in public health programmes and 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/l) 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 less than 0.01 µg/l. 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.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	FAO/WHO (2001) <i>Pesticide residues in food—2000 evaluations</i> WHO (2003) <i>Fenitrothion in drinking-water</i>

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/l can be calculated for fenitrothion on the basis of an ADI of 0–0.005 mg/kg body weight, based on a NOAEL of 0.5 mg/kg 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 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 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 upper limit of the ADI to drinking-water. However, because fenitrothion occurs at concentrations well below those of health concern, it is not considered necessary to derive a formal guideline value.

### **Fenoprop**

The half-lives for degradation of chlorophenoxy herbicides, including fenoprop (CAS No. 93-72-1), also known as 2,4,5-trichlorophenoxy propionic acid or 2,4,5-TP, in the environment are in the order of several days. Chlorophenoxy herbicides are not often found in food.

Guideline value	0.009 mg/l (9 µg/l)
Occurrence	Chlorophenoxy herbicides not frequently found in drinking-water; when detected, concentrations usually no greater than a few micrograms per litre
TDI	3 µg/kg body weight, based on a NOAEL of 0.9 mg/kg body weight for adverse effects on the liver in a study in which dogs were administered fenoprop in the diet for 2 years, with an uncertainty factor of 300 (100 for interspecies and intraspecies variation and 3 for limitations of the database)

Limit of detection	0.2 µg/l by either packed or capillary column GC with ECD
Treatment performance	0.001 mg/l should be achievable using GAC
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 10% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
Assessment date	1993
Principal reference	WHO (2003) <i>Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in drinking-water</i>

Chlorophenoxy herbicides, as a group, have been classified in Group 2B (possibly carcinogenic to humans) by IARC. However, the available data from studies in exposed populations and experimental 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 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.

### **Fluoride<sup>1</sup>**

Fluorine is a common element that is widely distributed in 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 groundwaters. In some 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 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 or 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 usually between 0.5 and 1 mg/l. The fluoride in final water is always present as fluoride ions, whether from natural sources or from artificial fluoridation.

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



## 12. CHEMICAL FACT SHEETS

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/l (1500 µg/l)
Occurrence	In groundwater, concentrations vary with the type of rock through which the water flows but do not usually exceed 10 mg/l; highest natural level reported is 2800 mg/l
Basis of guideline value derivation	Epidemiological evidence that concentrations above this value carry an increasing risk of dental fluorosis and that 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/l.
Limit of detection	0.01 mg/l by ion chromatography; 0.1 mg/l by ion-selective electrodes or the sulfo phenyl azo dihydroxy naphthalene disulfonic acid colorimetric method
Treatment performance	1 mg/l should be achievable using activated alumina (not a “conventional” treatment process, but relatively simple to install filters)
Additional comments	<p>A management guidance document on fluoride is available.</p> <p>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 concentrations lower than the guideline value.</p> <p>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.</p>
Assessment date	2003
Principal references	<p>Fawell et al. (2006) <i>Fluoride in drinking-water</i></p> <p>IPCS (2002) <i>Fluorides</i></p> <p>USNRC (2006) <i>Fluoride in drinking water</i></p> <p>WHO (2003) <i>Fluoride in drinking-water</i></p>

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—from high-fluoride coal, for example—is also absorbed, depending on the particle size and solubility of the fluoride compounds present. Absorbed fluoride is rapidly distributed throughout 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/l. 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/l, 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 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. The relationship between exposure and response for adverse effects in bone is frequently difficult to ascertain because of inadequacies in most of the epidemiological studies. IPCS 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 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 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/l 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/l.

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/l.

### 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.

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. 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.

### **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/l 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.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2004
Principal references	IPCS (2002) <i>Formaldehyde</i> WHO (2005) <i>Formaldehyde in drinking-water</i>

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/l for ingested formaldehyde has been established based on a NOEL of 260 mg/l 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 (for interspecies and 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.

### **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.

Reason for not establishing guideline values	Occur in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	FAO/WHO (1998) <i>Pesticide residues in food—1997 evaluations</i> IPCS (1994) <i>Glyphosate</i> WHO (2003) <i>Glyphosate and AMPA in drinking-water</i>

Glyphosate and AMPA have similar toxicological profiles, and both are considered to exhibit low toxicity. A health-based value of 0.9 mg/l can be derived based on the group ADI for AMPA alone or in combination with glyphosate of 0–0.3 mg/kg body weight, based upon a NOAEL of 32 mg/kg 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 (for interspecies and intraspecies variation).

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 formal guideline value for glyphosate and AMPA is not deemed necessary.

**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 or decreasing pH is 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	<i>Dichloroacetonitrile</i> : 0.02 mg/l (20 µg/l) The guideline value for dichloroacetonitrile is provisional owing to limitations of the toxicological database.
Guideline value	<i>Dibromoacetonitrile</i> : 0.07 mg/l (70 µg/l)
Occurrence	Concentrations of individual halogenated acetonitriles can exceed 0.01 mg/l, although levels of 0.002 mg/l or less are more usual
TDIs	<i>Dichloroacetonitrile</i> : 2.7 µg/kg body weight based on a LOAEL of 8 mg/kg 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 intraspecies and interspecies variation, the short duration of the study, the use of a minimal LOAEL and database deficiencies)  <i>Dibromoacetonitrile</i> : 11 µg/kg body weight, based on a NOAEL of 11.3 mg/kg body weight per day for decreased body weight in male rats in a 90-day drinking-water study and an uncertainty factor of 1000 (accounting for interspecies and intraspecies variation, subchronic to chronic extrapolation and database insufficiencies)
Limit of detection	0.03 µg/l by GC with ECD
Treatment performance	Reduction of organic precursors will reduce the formation of halogenated acetonitriles.
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 20% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
Assessment date	2003
Principal references	IPCS (2000) <i>Disinfectants and disinfectant by-products</i> WHO (2003) <i>Halogenated acetonitriles in drinking-water</i>
Reason for not establishing guideline values	Available data inadequate to permit derivation of health-based guideline values for <i>bromochloroacetonitrile</i> and <i>trichloroacetonitrile</i>
Assessment date	2003
Principal references	IPCS (2000) <i>Disinfectants and disinfectant by-products</i> WHO (2003) <i>Halogenated acetonitriles in drinking-water</i>

IARC has concluded that dichloroacetonitrile, dibromoacetonitrile, bromochloroacetonitrile 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 analysis 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 because cyanide, a metabolite of dibromoacetonitrile, induces male reproductive system toxicity and because of uncertainty regarding the significance of the testes effects observed in a 14-day 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/l was based on a developmental toxicity study in which trichloroacetonitrile was administered by gavage in tricapyrylin vehicle, and a re-evaluation judged this study to be unreliable in light of the finding in a more recent study that tricapyrylin potentiates the developmental and teratogenic effects of halogenated acetonitriles and alters the spectrum of malformations in the fetuses of treated dams.

### **Hardness**

Hardness in water is caused by a variety of dissolved polyvalent metallic ions, predominantly calcium and magnesium cations. It is usually expressed as milligrams of calcium carbonate per litre. Hardness is the traditional measure of the capacity of

water to react with soap, hard water requiring considerably more soap to produce a lather.

Reason for not establishing a guideline value	Not of health concern at levels found in drinking-water
Additional comments	May affect acceptability of drinking-water
Assessment date	1993, revised in 2011
Principal reference	WHO (2011) <i>Hardness in drinking-water</i>

Natural and treated waters have a wide range of mineral content, from very low levels in rainwater and naturally soft and softened water to higher levels in naturally hard waters. Bottled and packaged waters can be naturally mineralized or naturally soft or demineralized. Thus, the mineral consumption from drinking-water and cooking water will vary widely, depending upon location, treatment and water source.

The degree of hardness of drinking-water is important for aesthetic acceptability by consumers (see chapter 10) and for economic and operational considerations. Many hard waters are softened for those reasons using several applicable technologies. The choice of the most appropriate conditioning technology will depend on local circumstances (e.g. water quality issues, piping materials, corrosion) and will be applied either centrally or in individual homes as a consumer preference.

Consumers should be informed of the mineral composition of their water, whether or not it is modified. The contribution of drinking-water minerals to mineral nutrition should be considered where changes in supply are proposed or where less traditional sources, such as recycled water, seawater or brackish water, are processed and exploited for drinking-water. The treatments used remove most minerals, and stabilization of water is always necessary prior to distribution.

Drinking-water can be a contributor to calcium and magnesium intake and could be important for those who are marginal for calcium and magnesium. Where drinking-water supplies are supplemented with or replaced by demineralized water that requires conditioning, consideration should be given to adding calcium and magnesium salts to achieve concentrations similar to those that the population received from the original supply. Modification of calcium and magnesium concentrations in drinking-water for health reasons should comply with the technical requirements to provide water suitable for distribution.

Although there is evidence from epidemiological studies for a protective effect of magnesium or hardness on cardiovascular mortality, the evidence is being debated and does not prove causality. Further studies are being conducted. There are insufficient data to suggest either minimum or maximum concentrations of minerals at this time, as adequate intake will depend on a range of other factors. Therefore, no guideline values are proposed.

### ***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 nanogram per litre levels. Diet is considered to represent the major source of exposure to heptachlor, although intake is decreasing significantly, as its use has substantially declined.

Reason for not establishing a guideline value	Occur in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	FAO/WHO (1992) <i>Pesticide residues in food—1991 evaluations</i> FAO/WHO (1995) <i>Pesticide residues in food—1994 evaluations</i> WHO (2003) <i>Heptachlor and heptachlor epoxide in drinking-water</i>

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 (possibly carcinogenic to humans). A health-based value of 0.03 µg/l can be calculated for heptachlor and heptachlor epoxide on the basis of a PTDI of 0.1 µg/kg body weight, based on a NOAEL for heptachlor of 0.025 mg/kg 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 of health concern, it is not considered necessary to derive a formal guideline value. It should also be noted that concentrations below 0.1 µg/l are generally not achievable using conventional treatment technology.

### **Hexachlorobenzene**

The major agricultural application for hexachlorobenzene (CAS No. 118-74-1), or HCB, 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 physicochemical 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/l), in drinking-water supplies.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	IPCS (1997) <i>Hexachlorobenzene</i> WHO (2003) <i>Hexachlorobenzene in drinking-water</i>



IARC has evaluated the evidence for the carcinogenicity of HCB in animals and humans and assigned it to Group 2B (possibly carcinogenic to humans). HCB has been shown to induce tumours in three animal species and at a variety of sites. A health-based value of 1 µg/l 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 (tumorigenic dose<sub>05</sub>, or TD<sub>05</sub>) approach, a TDI of 0.16 µg/kg body weight can be calculated, which corresponds to a health-based value of approximately 0.05 µg/l, if one assumes a 1% allocation of the TDI to drinking-water. It should be noted that concentrations in food have been falling steadily, and this allocation factor may be considered very conservative.

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 formal guideline value for HCB in drinking-water. HCB is listed under the Stockholm Convention on Persistent Organic Pollutants.

### **Hexachlorobutadiene**

Hexachlorobutadiene, or HCB, 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/l have been reported in the effluents from chemical manufacturing plants. HCB is also found in air and food.

Guideline value	0.0006 mg/l (0.6 µg/l)
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/l
TDI	0.2 µg/kg body weight, based on a NOAEL of 0.2 mg/kg body weight per day for renal toxicity in a 2-year feeding study in rats, using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for limited evidence of carcinogenicity and genotoxicity of some metabolites)
Limit of detection	0.01 µg/l by GC-MS; 0.18 µg/l by GC with ECD
Treatment performance	0.001 mg/l should be achievable using GAC
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 10% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
Additional comments	The practical quantification limit for HCB is of the order of 2 µg/l, but concentrations in drinking-water can be controlled by specifying the HCB content of products coming into contact with it.
Assessment date	2003
Principal references	IPCS (1994) <i>Hexachlorobutadiene</i> WHO (2003) <i>Hexachlorobutadiene in drinking-water</i>

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 (not classifiable as to its carcinogenicity to humans). Positive and negative results for HCBD have been obtained in bacterial assays for point mutation; however, several metabolites have given positive results.

### **Hydrogen sulfide**

Hydrogen sulfide is a gas with an offensive “rotten eggs” odour that is detectable at very low concentrations, below 0.8 µg/m<sup>3</sup> 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 or chlorinated water.

Reason for not establishing a guideline value	Not of health concern at levels found in drinking-water
Additional comments	May affect acceptability of drinking-water
Assessment date	1993
Principal reference	WHO (2003) <i>Hydrogen sulfide in drinking-water</i>

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/m<sup>3</sup>. 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 can be easily detected in drinking-water by taste or odour (see chapter 10).

### **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/l 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.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal reference	WHO (2003) <i>Inorganic tin in drinking-water</i>

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

No increased incidence of tumours was observed in long-term carcinogenicity studies conducted in mice and rats fed tin(II) 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 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 body weight from a TDI of 2 mg/kg 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.

### **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.

Reason for not establishing a guideline value	Available data inadequate to permit derivation of health-based guideline value, and lifetime exposure to iodine through water disinfection is unlikely
Assessment date	1993
Principal reference	WHO (2003) <i>Iodine in drinking-water</i>

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, resulting in severe adverse effects on neurological development. In 1988, JECFA set a provisional maximum tolerable daily intake (PMTDI) for iodine of 1 mg/day (17 µg/kg 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.

### **Iron**

Iron is one of the most abundant metals in Earth's crust. It is found in natural fresh waters at levels ranging from 0.5 to 50 mg/l. 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.

Reason for not establishing a guideline value	Not of health concern at levels found in drinking-water
Additional comments	May affect acceptability of drinking-water
Assessment date	1993
Principal reference	WHO (2003) <i>Iron in drinking-water</i>

Iron is an essential element in human nutrition, particularly in the iron(II) oxidation state. 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 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/l, 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.

### **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/l (9 µg/l)
Occurrence	Has been detected in surface water and groundwater, usually at concentrations below 0.1 µg/l; levels above 0.1 µg/l have occasionally been detected in drinking-water
TDI	3 µg/kg body weight based on a NOAEL of approximately 3 mg/kg 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 interspecies and intraspecies variation and 10 for evidence of non-genotoxic carcinogenicity in rats)
Limit of detection	10–100 ng/l by reversed-phase HPLC followed by UV or electrochemical detection
Treatment performance	0.1 µg/l should be achievable using ozonation
Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day

Assessment date	1993
Principal reference	WHO (2003) <i>Isoproturon in drinking-water</i>

Isoproturon is of low acute toxicity and low to moderate toxicity following short-term 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.

### 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 has largely been 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; in most countries, lead levels in blood are also declining unless there are specific sources, such as dust from leaded paint or household recycling of lead-containing materials. Lead is rarely present in tap water as a result of its dissolution from natural sources; rather, its presence is primarily from corrosive water effects on 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. Free chlorine residuals in drinking-water tend to form more insoluble lead-containing sediments, whereas chloramine residuals may form more soluble sediments in lead pipe.

Provisional guideline value	0.01 mg/l (10 µg/l) The guideline value is provisional on the basis of treatment performance and analytical achievability.
Occurrence	Concentrations in drinking-water are generally below 5 µg/l, although much higher concentrations (above 100 µg/l) have been measured where lead fittings are present. The primary source of lead is from service connections and plumbing in buildings; therefore, lead should be measured at the tap. Lead concentrations can also vary according to the period in which the water has been in contact with the lead-containing materials.
Basis of guideline value derivation	The guideline value was previously based on a JECFA PTWI, which has since been withdrawn, and no new PTWI has been established, on the basis that there does not appear to be a threshold for the key effects of lead. However, substantial efforts have been made to reduce lead exposure from a range of sources, including drinking-water. Because it is extremely difficult to achieve a lower concentration by central conditioning, such as phosphate dosing, the guideline value is maintained at 10 µg/l but is designated as provisional on the basis of treatment performance and analytical achievability.

Limit of detection	1 µg/l by AAS; practical quantification limit in the region of 1–10 µg/l
Treatment performance	Not a raw water contaminant; treatment not applicable
Additional comments	<p>Infants and children are considered to be the most sensitive subgroups of the population.</p> <p>Lead is exceptional compared with other chemical hazards, 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 value immediately. Meanwhile, all other practical measures to reduce total exposure to lead, including corrosion control, should be implemented.</p>
Assessment date	2011
Principal reference	FAO/WHO (2011) <i>Evaluation of certain food additives and contaminants</i> WHO (2011) <i>Lead in drinking-water</i>

Exposure to lead is associated with a wide range of effects, including various neurodevelopmental effects, mortality (mainly due to cardiovascular diseases), impaired renal function, hypertension, impaired fertility and adverse pregnancy outcomes. Impaired neurodevelopment in children is generally associated with lower blood lead concentrations than the other effects, the weight of evidence is greater for neurodevelopmental effects than for other health effects and the results across studies are more consistent than those for other effects. For adults, the adverse effect associated with lowest blood lead concentrations for which the weight of evidence is greatest and most consistent is a lead-associated increase in systolic blood pressure. JECFA concluded that the effects on neurodevelopment and systolic blood pressure provided the appropriate bases for dose–response analyses.

Based on the dose–response analyses, JECFA estimated that the previously established PTWI of 25 µg/kg body weight is associated with a decrease of at least 3 intelligence quotient (IQ) points in children and an increase in systolic blood pressure of approximately 3 mmHg (0.4 kPa) in adults. These changes are important when viewed as a shift in the distribution of IQ or blood pressure within a population. JECFA therefore concluded that the PTWI could no longer be considered health protective, and it was withdrawn.

Because the dose–response analyses do not provide any indication of a threshold for the key effects of lead, JECFA concluded that it was not possible to establish a new PTWI that would be considered to be health protective. JECFA reaffirmed that because of the neurodevelopmental effects, fetuses, infants and children are the subgroups that are most sensitive to lead.

It needs to be recognized that lead is exceptional compared with other chemical hazards, in that most lead in drinking-water arises from plumbing in buildings, and the remedy consists principally of removing plumbing and fittings containing lead, which requires much time and money. It is therefore emphasized that all other practical measures to reduce total exposure to lead, including corrosion control, should be implemented.

**Lindane**

Lindane ( $\gamma$ -hexachlorocyclohexane;  $\gamma$ -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.

Guideline value	0.002 mg/l (2 $\mu$ g/l)
Occurrence	Has been detected in both surface water and groundwater, usually at concentrations below 0.1 $\mu$ g/l, although concentrations as high as 12 $\mu$ g/l have been measured in wastewater-contaminated rivers
ADI	0–0.005 mg/kg body weight on the basis of a NOAEL of 0.47 mg/kg 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 (for interspecies and intraspecies variation)
Limit of detection	0.01 $\mu$ g/l using GC
Treatment performance	0.1 $\mu$ g/l should be achievable using GAC
Guideline value derivation	
• allocation to water	1% of upper limit of ADI
• weight	60 kg adult
• consumption	2 litres/day
Additional comments	It should be noted that concentrations in food have been falling steadily, and the 1% allocation factor may be considered very conservative.
Assessment date	2003
Principal references	FAO/WHO (2003) <i>Pesticide residues in food—2002 evaluations</i> WHO (2003) <i>Lindane in drinking-water</i>

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, as it is a consequence of accumulation of  $\alpha_{2u}$ -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 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 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.

### **Malathion**

Malathion (CAS No. 121-75-5) is commonly used to control mosquitoes 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/l.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	FAO/WHO (1998) <i>Pesticide residues in food—1997 evaluations</i> WHO (2003) <i>Malathion in drinking-water</i>

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/l can be calculated for malathion based on an allocation of 10% of the upper limit of the JMPR ADI—based on a NOAEL of 29 mg/kg body weight per day in a 2-year study of toxicity and carcinogenicity in rats, using an uncertainty factor of 100 for interspecies and intraspecies variation and supported by a NOAEL of 25 mg/kg 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 upper limit of 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 formal guideline value for malathion in drinking-water.

### **Manganese**

Manganese is one of the most abundant metals in 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, methylcyclopentadienyl manganese tricarbonyl, or MMT, as an octane



enhancer in petrol in North America. Manganese greensands are used in some locations for potable water treatment. 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. Manganese occurs naturally in many food sources, and the greatest exposure to manganese is usually from food.

Reason for not establishing a guideline value	Not of health concern at levels found in drinking-water
Additional comments	May affect acceptability of drinking-water
Assessment date	2003, revised 2011
Principal references	IPCS (1999) <i>Manganese and its compounds</i> WHO (2011) <i>Manganese in drinking-water</i>

Manganese is an essential element for humans and animals. Although there have been epidemiological studies that report adverse neurological effects following extended exposure to very high levels in drinking-water, 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. Experimental animal data, especially rodent data, are not appropriate for human risk assessment because the physiological requirements for manganese vary among different species. Further, rodents are of limited value in assessing 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.

A health-based value of 0.4 mg/l can be derived for manganese 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, using an uncertainty factor of 3 to take into consideration the possible increased bioavailability of manganese from water, allocating 20% of the TDI to drinking-water and assuming the consumption of 2 litres of water per day by a 60 kg adult. However, as this health-based value is well above concentrations of manganese normally found in drinking-water, it is not considered necessary to derive a formal guideline value.

It is also noted that concentrations below the health-based value may give rise to black deposits in water mains over an extended period (see chapter 10).

### **MCPA**

MCPA, or 4-(2-methyl-4-chlorophenoxy)acetic acid (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.

## GUIDELINES FOR DRINKING-WATER QUALITY

Guideline value	0.002 mg/l (2 µg/l)
Occurrence	Not frequently detected in drinking-water; has been measured in surface water and groundwater at concentrations below 0.54 and 5.5 µg/l, respectively
TDI	0.5 µg/kg body weight, based on a NOAEL of 0.15 mg/kg 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 interspecies and intraspecies variation and 3 for inadequacies of the database)
Limit of detection	0.01 µg/l by GC-MS and GC with ECD
Treatment performance	0.1 µg/l should be achievable using GAC or ozonation
Guideline value derivation	<ul style="list-style-type: none"> <li>• allocation to water 10% of TDI</li> <li>• weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>
Assessment date	1993
Principal reference	WHO (2003) <i>MCPA in drinking-water</i>

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.

### **Mecoprop**

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

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

Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	1993
Principal reference	WHO (2003) <i>Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in drinking-water</i>

Chlorophenoxy herbicides, as a group, have been classified in Group 2B (possibly carcinogenic to humans) by IARC. However, the available data from studies in exposed populations and experimental 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-term and long-term studies include decreased relative kidney weight (rats and dogs), increased relative liver weight (rats), effects on blood parameters (rats and dogs) and depressed body weight gain (dogs).

### **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  $\text{Hg}^{2+}$ . 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/l (6 $\mu\text{g}/\text{l}$ ) for inorganic mercury
Occurrence	Mercury is present in the inorganic form in surface water and groundwater at concentrations usually below 0.5 $\mu\text{g}/\text{l}$ , although local mineral deposits may produce higher levels in groundwater
TDI	2 $\mu\text{g}/\text{kg}$ body weight for inorganic mercury based on a NOAEL of 0.23 mg/kg body weight per day for kidney effects in a 26-week study in rats and applying an uncertainty factor of 100 (for interspecies and intraspecies variation) after adjusting for daily dosing
Limit of detection	0.05 $\mu\text{g}/\text{l}$ by cold vapour AAS; 0.6 $\mu\text{g}/\text{l}$ by ICP; 5 $\mu\text{g}/\text{l}$ by flame AAS
Treatment performance	It should be possible to achieve a concentration below 1 $\mu\text{g}/\text{l}$ by treatment of raw waters that are not grossly contaminated with mercury using methods that include coagulation/sedimentation/filtration, PAC and ion exchange.

Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Additional comments	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 body weight per day in a 2-year NTP study in rats.  The current 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.
Assessment date	2004
Principal references	IPCS (2003) <i>Elemental mercury and inorganic mercury compounds</i> WHO (2005) <i>Mercury in drinking-water</i>

The toxic effects of inorganic mercury compounds are seen mainly in the kidney in both humans and laboratory animals following short-term 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.

### **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/l (20 µg/l)
Occurrence	Detected occasionally in drinking-water, at concentrations as high as 300 µg/l in rural areas
TDI	5 µg/kg body weight, based on a systemic NOAEL of 5 mg/kg body weight in a teratology study in rabbits, with an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 reflecting concern for threshold carcinogenicity and the limited database)
Limit of detection	0.001–0.01 µg/l by GC
Treatment performance	0.1 µg/l should be achievable using GAC

Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	1993
Principal reference	WHO (2003) <i>Methoxychlor in drinking-water</i>

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 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.

### **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/l, with highest levels in summer. The general population can come into contact with methyl parathion via air, water or food.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	FAO/WHO (1996) <i>Pesticide residues in food—1995 evaluations</i> . IPCS (1992) <i>Methyl parathion</i> WHO (2003) <i>Methyl parathion in drinking-water</i>

A NOAEL of 0.3 mg/kg 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/l can be calculated for methyl parathion on the basis of an ADI of 0–0.003 mg/kg body weight, based on a NOAEL of 0.25 mg/kg 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 for interspecies and intraspecies variation. As the toxicological end-points seen in experimental 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 upper limit of the ADI. As the health-based value is much higher than concentrations of methyl parathion 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 formal guideline value for methyl parathion is not deemed necessary.

### ***Methyl tertiary-butyl ether***

The major use of methyl *tert*-butyl ether, or MTBE, is as a gasoline additive. Surface water can be contaminated by gasoline spills; however, owing to the high volatility of MTBE, most is lost to evaporation. 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 nanogram to microgram per litre range.

Reason for not establishing a guideline value	Any guideline that would be derived would be significantly higher than concentrations at which MTBE would be detected by odour
Assessment date	2004
Principal references	IPCS (1998) <i>Methyl tertiary-butyl ether</i> WHO (2005) <i>Methyl tertiary-butyl ether (MTBE) in drinking-water</i>

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, owing 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/l is the lowest level eliciting a response in a study using taste- and odour-sensitive participants).

### **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, photodegradation 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/l (10 µg/l)
Occurrence	Detected in surface water and groundwater at concentrations that can exceed 10 µg/l
TDI	3.5 µg/kg body weight, based on a NOAEL of 3.5 mg/kg 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 interspecies and intraspecies variation and 10 reflecting some concern regarding carcinogenicity)
Limit of detection	0.75–0.01 µg/l by GC with nitrogen–phosphorus detection
Treatment performance	0.1 µg/l should be achievable using GAC
Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	1993
Principal reference	WHO (2003) <i>Metolachlor in drinking-water</i>

In a 1-year study in 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 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.

### **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/l (6 µg/l)
Occurrence	Concentrations in water rarely exceed 1 µg/l
TDI	2 µg/kg body weight, based on a NOAEL for reproductive toxicity in the rat of 0.2 mg/kg body weight, with an uncertainty factor of 100 (for inter-species and intraspecies variation)
Limit of detection	0.01 µg/l by GC-MS
Treatment performance	0.001 mg/l should be achievable using GAC
Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	1993
Principal reference	WHO (2003) <i>Molinate in drinking-water</i>

On the basis of the limited information available, molinate does not seem to be carcinogenic or mutagenic in experimental 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.

### **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. Concentrations in drinking-water are usually less than 0.01 mg/l, although concentrations as high as 200 µg/l have been reported in areas near mining sites.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	1993, revised in 2011
Principal references	WHO (2011) <i>Molybdenum in drinking-water</i>

Molybdenum is considered to be an essential element, with an estimated daily requirement of 0.1–0.3 mg for adults.

As molybdenum occurs at very low concentrations in drinking-water, it is not considered necessary to set a formal guideline value. For guidance purposes, a health-based value can be derived.

In a 2-year study of humans exposed via drinking-water, the NOAEL was found to be 0.2 mg/l, but there are some concerns about the quality of this study. As molybdenum is an essential element, a factor of 3 is considered to be adequate to reflect intraspecies variation. This gives a health-based value of 0.07 mg/l (rounded figure), which is in the same range as that derived on the basis of the results of toxicological studies in experimental animals and is consistent with the essential daily requirement for molybdenum.



**Monochloroacetic acid**

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

Guideline value	0.02 mg/l (20 µg/l)
Occurrence	Present in surface water–derived drinking-water at concentrations up to 82 µg/l (mean 2.1 µg/l)
TDI	3.5 µg/kg body weight, based on a LOAEL of 3.5 mg/kg 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, using an uncertainty factor of 1000 (100 for interspecies 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/l by GC with ECD; 5 µg/l by GC-MS
Treatment performance	No information available
Guideline value derivation	
• allocation to water	20% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	2003
Principal reference	WHO (2003) <i>Monochloroacetic acid in drinking-water</i>

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.

**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/l in some potable water sources (maximum 5 µg/l) in Canada. The major source of human exposure is probably air.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern, and health-based value would far exceed lowest reported taste and odour threshold
Assessment date	2003
Principal reference	WHO (2003) <i>Monochlorobenzene in drinking-water</i>

MCB is of low acute toxicity. Oral exposure to high doses of MCB results in effects mainly on 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/l can be calculated for MCB on the basis of a TDI of 85.7 µg/kg 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 of health concern, it is not considered necessary to derive a formal 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.

### **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/l. Five drinking-water samples from different Japanese cities contained MX at concentrations ranging from less than 3 to 9 ng/l.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	IPCS (2000) <i>Disinfectants and disinfectant by-products</i> WHO (2003) <i>MX in drinking-water</i>

MX is a potent mutagen in bacteria and in cells *in vitro* and has undergone a lifetime 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 (possibly carcinogenic to humans) on the basis of rat tumorigenicity and its strong mutagenicity.

A health-based value of 1.8 µg/l 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.

### **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 occurs naturally in groundwater is mobilized or where there is use of certain types of kettles,

## 12. CHEMICAL FACT SHEETS

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.

Guideline value	0.07 mg/l (70 µg/l)
Occurrence	Concentration in drinking-water normally less than 0.02 mg/l, although nickel released from taps and fittings may contribute up to 1 mg/l; in special cases of release from natural or industrial nickel deposits in the ground, concentrations in drinking-water may be higher
TDI	12 µg/kg body weight, derived from a LOAEL established after oral provocation of fasted patients with an empty stomach
Limit of detection	0.1 µg/l by ICP-MS; 0.5 µg/l by flame AAS; 10 µg/l by ICP-AES
Treatment performance	20 µg/l 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 value derivation	
<ul style="list-style-type: none"> <li>● allocation to water</li> <li>● weight</li> <li>● consumption</li> </ul>	20% of TDI 60 kg adult 2 litres/day
Additional comments	<p>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. Basing 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.</p> <p>A general toxicity value of 130 µg/l 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.</p>
Assessment date	2004
Principal reference	WHO (2005) <i>Nickel in drinking-water</i>

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.

**Nitrate and nitrite<sup>1</sup>**

Nitrate ( $\text{NO}_3^-$ ) 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 ( $\text{NO}_2^-$ ) is not usually present in significant concentrations except in a reducing environment, as nitrate is the more stable oxidation state. It can be formed by the microbial reduction of nitrate and *in vivo* by reduction from ingested 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-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 values	<p><i>Nitrate:</i> 50 mg/l as nitrate ion (or 11 mg/l as nitrate-nitrogen) to protect against methaemoglobinaemia in bottle-fed infants (short-term exposure)</p> <p><i>Nitrite:</i> 3 mg/l as nitrite ion (or 0.9 mg/l as nitrite-nitrogen) to protect against methaemoglobinaemia in bottle-fed infants (short-term exposure)</p> <p><i>Combined nitrate plus nitrite:</i> The sum of the ratios of the concentrations as reported or detected in the sample of each to its guideline value should not exceed 1.</p>
Occurrence	<p>In most countries, nitrate levels in drinking-water derived from surface water do not exceed 10 mg/l, although nitrate levels in well water often exceed 50 mg/l; nitrite levels are normally lower, less than a few milligrams per litre</p>
Basis of guideline value derivation	<p><i>Nitrate (bottle-fed infants):</i> In epidemiological studies, methaemoglobinaemia was not reported in infants in areas where drinking-water consistently contained less than 50 mg of nitrate per litre</p> <p><i>Nitrite (bottle-fed infants):</i> Application of body weight of 5 kg for an infant and drinking-water consumption of 0.75 litre to lowest level of the dose range associated with methaemoglobinaemia, 0.4 mg/kg body weight. This is supported by accepting a relative potency for nitrite and nitrate with respect to methaemoglobin formation of 10:1 (on a molar basis).</p>

<sup>1</sup> As nitrate and nitrite are chemicals of significant concern in some natural waters, the chemical fact sheet on nitrate and nitrite has been expanded.

## 12. CHEMICAL FACT SHEETS

Limit of detection	0.005–0.01 mg/l (nitrite) by a molecular absorption spectrometric method; 0.01–1 mg/l (nitrate) by spectrometric techniques; 0.022 mg/l (nitrate) and 0.035 mg/l (nitrite) by ion chromatography; 0.1 mg/l (nitrate) and 0.05 mg/l (nitrite) by LC
Treatment performance	<p><i>Nitrate</i>: 5 mg/l or lower should be achievable using biological denitrification (surface waters) or ion exchange (groundwaters)</p> <p><i>Nitrite</i>: 0.1 mg/l should be achievable using chlorination (to form nitrate)</p>
Additional comments	<p>Nitrite can occur in the distribution system at higher concentrations when chloramination is used, but the occurrence is almost invariably sporadic. Methaemoglobinaemia 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.</p> <p>Methaemoglobinaemia in infants appears to be associated with simultaneous diarrhoeal disease. Authorities should therefore be <b>all the more vigilant</b> that water to be used for bottle-fed infants is microbiologically safe when nitrate is present at concentrations near the guideline value or in the presence of endemic infantile diarrhoea. Water should not be used for bottle-fed infants if the concentration of nitrate is above 100 mg/l but can be used if the concentration is between 50 and 100 mg/l if the water is microbiologically safe and there is increased vigilance by medical authorities.</p> <p>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 can be taken to modify the treatment train or water chemistry in order to minimize nitrite formation. Efficient disinfection must never be compromised.</p> <p>The occurrence of nitrite in the distribution system as a consequence of chloramine use will be intermittent, and average exposures over time should not exceed about 0.2 mg/l.</p>
Assessment date	1998, revised in 2007 and 2010
Principal references	<p>FAO/WHO (2002) <i>Evaluation of certain food additives</i></p> <p>FAO/WHO (2003) Nitrite (and potential endogenous formation of <i>N</i>-nitroso compounds)</p> <p>Schmoll et al. (2006) <i>Protecting groundwater for health</i></p> <p>WHO (2011) <i>Nitrate and nitrite in drinking-water</i></p>

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 endogenous formation of nitrate from nitric oxide and protein breakdown as part of normal metabolism. 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 or nitrite 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, as rats may not actively secrete nitrate in their saliva.

Nitrate probably has a role in protecting the gastrointestinal tract against a variety of gastrointestinal pathogens, as nitrous oxide and acidified nitrite have antibacterial properties. It may have other beneficial physiological roles. There may therefore be a benefit from exogenous nitrate uptake, and there remains a need to balance the potential risks with the potential benefits.

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 may include individuals using antacids, particularly those that block acid secretion.

In humans, methaemoglobinaemia is 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, thus 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 in infants 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 levels associated with drinking-water nitrate, 97% of cases occurred at concentrations in excess of 44.3 mg/l, with clinical symptoms associated with the higher concentrations. The affected individuals were almost exclusively under 3 months of age.

Although drinking-water nitrate may be an important risk factor for methaemoglobinaemia in bottle-fed infants, there is compelling evidence that the risk of methaemoglobinaemia is primarily increased in the presence of simultaneous gastrointestinal infections, which increase endogenous nitrite 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 secondary 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. Moderate consumption of a number of dietary antioxidant components, such as ascorbic acid and green tea, appears 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 high nitrate intake and simultaneous iodine deficiency, although the nitrate intakes at which this becomes significant are uncertain.

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 has been identified.

In some studies on 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. 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, as 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/l as nitrate (or 11 mg/l if reported as nitrate-nitrogen) 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.

The guideline value for nitrite of 3 mg/l as nitrite (or 0.9 mg/l if reported as nitrite-nitrogen) is based on human data showing that doses of nitrite that cause methaemoglobinaemia in infants range from 0.4 mg/kg body weight to more than 200 mg/kg body weight. By applying the lowest level of the range (0.4 mg/kg 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/l (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 1:

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

For chronic exposure, JECFA proposed an ADI of 0–3.7 mg/kg body weight for nitrate and an ADI of 0–0.07 mg/kg body weight for nitrite, expressed as nitrite ion. The value for nitrate is based on a NOEL of 370 mg/kg 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 JECFA ADI for nitrite was based on effects on heart and lung in a 2-year study in rats using a safety factor of 100. However, owing to the uncertainty surrounding the susceptibility of humans compared with experimental animals, this value was considered provisional and has now been suspended and is being subjected to review in light of evidence on the differences in nitrite metabolism between laboratory rodents and humans.

### Practical considerations

The most appropriate means of controlling nitrate concentrations, particularly in groundwater, is the prevention of contamination. 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 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*.

### **Nitritotriacetic acid**

Nitritotriacetic acid, or 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/l (200 µg/l)
Occurrence	Concentrations in drinking-water usually do not exceed a few micrograms per litre, although concentrations as high as 35 µg/l have been measured
TDI	10 µg/kg body weight, based on nephritis and nephrosis in a 2-year study in rats and using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for carcinogenic potential at high doses)
Limit of detection	0.2 µg/l using GC with a nitrogen-specific detector
Treatment performance	No information found on removal from water
Guideline value derivation	
• allocation to water	50% of TDI
• weight	60 kg adult
• consumption	2 litres/day

Assessment date	1993
Principal reference	WHO (2003) <i>Nitritotriacetic acid in drinking-water</i>

NTA is not metabolized in experimental animals and is rapidly eliminated, although some may be briefly retained in bone. It is of low acute toxicity to experimental 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 (possibly carcinogenic to humans). 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.

### **Nitrobenzene**

Nitrobenzene is used primarily in the production of aniline, but it is also used as a solvent, as an ingredient of metal polishes and soaps and in the synthesis of other organic compounds, including acetaminophen. Nitrobenzene can be released to water during these production processes.

Concentrations of nitrobenzene in environmental samples, such as surface water, groundwater and air, are generally low, except in areas with industrial pollution. Based on limited data, it appears that the potential for contamination is greater for groundwater than for surface water.

The general population can be exposed to variable concentrations of nitrobenzene in air and possibly drinking-water. Only populations in the vicinity of manufacturing activities and petroleum refining plants are likely to have any significant exposure to nitrobenzene; however, people living in and around abandoned hazardous waste sites may also have potential for higher exposure, due to possible groundwater and soil contamination and uptake of nitrobenzene by plants.

Reason for not establishing a guideline value	Rarely found in drinking-water at concentrations of health concern
Assessment date	2009
Principal reference	WHO (2009) <i>Nitrobenzene in drinking-water</i>

Nitrobenzene is toxic to humans by the inhalation, dermal and oral routes of exposure. The main systemic effect associated with human exposure to nitrobenzene is methaemoglobinaemia. Although some recent studies have reported positive results in mutagenicity tests, it cannot be excluded that nitrobenzene is a non-genotoxic chemical. No long-term oral administration studies are available. Based on inhalation studies, IARC concluded that there was inadequate evidence in humans but sufficient evidence in experimental animals for the carcinogenicity of nitrobenzene and classified nitrobenzene in Group 2B (possibly carcinogenic to humans).

Because nitrobenzene occurrence in drinking-water at concentrations above trace levels is infrequent, it is not considered necessary to derive a formal guideline value. However, health-based values can be calculated to provide guidance in the event

of spills and where there are higher concentrations in industrial areas. Two health-based values are derived based on the limited available information: one for short-term exposure (30 µg/l) and the other for long-term exposure (8–63 µg/l, depending on end-point and approach used). It should be emphasized that the derivation of the long-term health-based values includes large uncertainties because of the dose metric conversion from inhalation studies and the possibility of increased metabolism to aniline in the gastrointestinal tract.

It should be emphasized that nitrobenzene is a potent methaemoglobinaemic agent in humans, which is of particular concern for bottle-fed infants. Currently, data are not adequate to determine a separate health-based value for this end-point.

It should also be noted that the reported odour threshold for nitrobenzene in water is 30–110 µg/l.

### ***N-Nitrosodimethylamine***

*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 affected by wastewater discharges) and, to some extent, chlorination. NDMA can also be formed as a by-product of anion exchange treatment of water.

Guideline value	0.0001 mg/l (0.1 µg/l)
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/l have been measured in the distribution system, but concentrations in water at the treatment plant are generally less than 0.01 µg/l
Basis of guideline value 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/l by capillary column GC and chemical ionization tandem MS; 0.4 ng/l by capillary column GC and high-resolution MS; 0.7–1.6 ng/l by GC-MS and ammonia positive chemical ionization detection
Treatment performance	The most common process for NDMA removal is UV irradiation. A concentration below 0.005 µg/l 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.
Assessment date	2006
Principal references	IPCS (2002) <i>N-Nitrosodimethylamine</i> WHO (2008) <i>N-Nitrosodimethylamine in drinking-water</i>

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 O<sup>6</sup>-methylguanine as the likely proximal carcinogenic agent. As a consequence of the clear evidence of carcinogenicity, there have been few studies of other possible toxicity 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.

### **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.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	FAO/WHO (1996) <i>Pesticide residues in food—1995 evaluations</i> WHO (2003) <i>Parathion in drinking-water</i>

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/l can be calculated for parathion on the basis of an ADI of 0–0.004 mg/kg 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 next higher dose, and using an uncertainty factor of 100 for interspecies and intraspecies variation. Lower NOAELs in experimental 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 body weight per day.

Intake of parathion from all sources is generally low and well below the upper limit of the ADI. As the health-based value is much higher than concentrations of parathion 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 formal guideline value for parathion is not deemed necessary.

### **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.

Guideline value	0.02 mg/l (20 µg/l)
Occurrence	Rarely found in drinking-water in the limited studies available
TDI	5 µg/kg body weight, based on evidence of slight liver toxicity even at the lowest dose tested (5 mg/kg body weight) in a long-term rat feeding study, with an uncertainty factor of 1000 (100 for interspecies 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/l by GC-MS
Treatment performance	1 µg/l should be achievable using GAC
Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	1993
Principal reference	WHO (2003) <i>Pendimethalin in drinking-water</i>

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.

### **Pentachlorophenol**

Pentachlorophenol (CAS No. 87-86-5), or PCP, 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 contamination of drinking-water by PCP or exposure from log homes treated with PCP.

## GUIDELINES FOR DRINKING-WATER QUALITY

Provisional guideline value	0.009 mg/l (9 µg/l) 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/l, although much higher concentrations in groundwater may be measured under certain conditions
Basis of guideline value derivation	Multistage modelling of tumour incidence in an NTP bioassay without incorporation of a body surface area correction, recognizing that there are interspecies differences in metabolism between experimental 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/l by GC with ECD
Treatment performance	0.4 µg/l should be achievable using GAC
Additional comments	The concentration of PCP associated with a 10 <sup>-5</sup> upper-bound excess lifetime cancer risk is similar to the guideline value established in the second edition, so that guideline value is retained.
Assessment date	1998
Principal reference	WHO (2003) <i>Pentachlorophenol in drinking-water</i>

IARC classified PCP in Group 2B (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.

### **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.

Reason for not establishing a guideline value	Taste and odour will in most cases be detectable at concentrations below those of health concern, particularly with short-term exposure
Assessment date	2004
Principal reference	WHO (2005) <i>Petroleum products in drinking-water</i>

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. However,

a number of the most soluble aromatic hydrocarbons will be detectable by taste 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 total petroleum hydrocarbons 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.

### **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).

Reason for not establishing a guideline value	Not of health concern at levels found in drinking-water
Additional comments	An important operational water quality parameter
Assessment date	1993
Principal reference	WHO (2007) <i>pH in drinking-water</i>

### **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.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal references	FAO/WHO (2000) <i>Pesticide residues in food—1999 evaluations</i> WHO (2003) <i>2-Phenylphenol and its sodium salt in drinking-water</i>

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 concluded that 2-phenylphenol is unlikely to represent a carcinogenic risk to humans. Although a working group convened by IARC 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/l can be calculated for 2-phenylphenol on the basis of an ADI of 0–0.4 mg/kg body weight, based on a NOAEL of 39 mg/kg body weight per day in a 2-year toxicity study on the basis of 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 for interspecies and intraspecies variation. Because of its low toxicity, however, the health-based value derived for 2-phenylphenol is much higher than concentrations of 2-phenylphenol 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 formal guideline value for 2-phenylphenol is not deemed necessary.

### **Polynuclear aromatic hydrocarbons**

Polynuclear aromatic hydrocarbons, or 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 char-broiling, grilling,



## 12. CHEMICAL FACT SHEETS

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	<i>Benzo[a]pyrene</i> : 0.0007 mg/l (0.7 µg/l)
Occurrence	PAH levels in uncontaminated groundwater usually in range 0–5 ng/l; concentrations in contaminated groundwater may exceed 10 µg/l; typical concentration range for sum of selected PAHs in drinking-water is from about 1 ng/l to 11 µg/l
Basis of guideline value 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 benzo[a]pyrene 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/l by GC-MS and reversed-phase HPLC with a fluorescence detector
Treatment performance	0.05 µg/l should be achievable using coagulation
Additional comments	The presence of significant concentrations of benzo[a]pyrene 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.
Assessment date	1998
Principal reference	WHO (2003) <i>Polynuclear aromatic hydrocarbons in drinking-water</i>
Reason for not establishing a guideline value	<i>Fluoranthene</i> : Occurs in drinking-water at concentrations well below those of health concern
Assessment date	1998
Principal reference	WHO (2003) <i>Polynuclear aromatic hydrocarbons in drinking-water</i>

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 benzo[a]pyrene, 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 that of benzo[a]pyrene.

A health-based value of 4 µg/l can be calculated for fluoranthene on the basis of a NOAEL of 125 mg/kg 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 10 000 (100 for interspecies and intraspecies variation, 10 for the use of a subchronic study and inadequate database and 10 because of clear evidence of co-carcinogenicity with benzo[*a*]pyrene 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 formal guideline value for fluoranthene is not deemed necessary.

### **Potassium**

Potassium is an essential element in humans and is seldom, if ever, found in drinking-water at levels that could be a concern for healthy humans. The recommended daily requirement is greater than 3000 mg. Potassium occurs widely in the environment, including all natural waters. It can also occur in drinking-water as a consequence of the use of potassium permanganate as an oxidant in water treatment. In some countries, potassium chloride is being used in ion exchange for household water softening in place of, or mixed with, sodium chloride, so potassium ions would exchange with calcium and magnesium ions. Possible replacement or partial replacement of sodium salts with potassium salts for conditioning desalinated water has been suggested. The latter seems to be an unlikely development at this stage, in view of the cost difference.

Reason for not establishing a guideline value	Occurs in drinking-water at concentrations well below those of health concern
Assessment date	2009
Principal reference	WHO (2009) <i>Potassium in drinking-water</i>

Currently, there is no evidence that potassium levels in municipally treated drinking-water, even water treated with potassium permanganate, are likely to pose any risk for the health of consumers. It is not considered necessary to establish a health-based guideline value for potassium in drinking-water.

Although potassium may cause some health effects in susceptible individuals, potassium intake from drinking-water is well below the level at which adverse health effects may occur. Health concerns would be related to the consumption of drinking-water treated by potassium-based water treatment (principally potassium chloride for regeneration of ion exchange water softeners), affecting only individuals in high-risk groups (i.e. individuals with kidney dysfunction or other diseases, such as heart disease, coronary artery disease, hypertension, diabetes, adrenal insufficiency, pre-existing hyperkalaemia; people taking medications that interfere with normal potassium-dependent functions in the body; and older individuals or infants). It is recommended that susceptible individuals seek medical advice to determine whether they should avoid the consumption of water (for drinking or cooking) treated by water softeners using potassium chloride.

When high-risk individuals have been advised by a physician to avoid elevated potassium intake from water, the recommended strategy is to limit the addition of potassium to water that will be ingested or to avoid ingesting such water. This can be done by having a proportion of the water bypass the softener altogether; this approach is recommended by several countries. Although technologies are available to remove potassium, they are generally more expensive and redundant when combined with the softening treatment.

### **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.

Reason for not establishing a guideline value	Readily transformed into metabolites that are more toxic; a guideline value for the parent compound is considered inappropriate, and there are inadequate data to enable the derivation of guideline values for the metabolites
Assessment date	2003
Principal reference	WHO (2003) <i>Propanil in drinking-water</i>

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 guideline values for them. Authorities should consider the possible presence in water of more toxic environmental metabolites.

### **Selenium**

Selenium is present in 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 for the general population. Levels in food also vary greatly according to geographical area of production. However, even in high-selenium areas, the relative contribution of selenium from drinking-water is likely to be small in comparison with that from locally produced food.

Provisional guideline value	0.04 mg/l (40 µg/l) The guideline value is designated as provisional because of the uncertainties inherent in the scientific database.
Occurrence	Most drinking-water contains concentrations of selenium that are much lower than 10 µg/l, except in certain seleniferous areas

## GUIDELINES FOR DRINKING-WATER QUALITY

Basis of guideline value derivation	An allocation of 20% of the upper tolerable intake of 400 µg/day to drinking-water provides a sensible balance that will assist regulators and suppliers in making decisions about whether further action is needed
Limit of detection	0.5 µg/l by hydride generation AAS
Treatment performance	Selenium is not removed by conventional treatment processes; significant removals of selenium from water using activated alumina adsorption, ion exchange, reverse osmosis and nanofiltration have been reported.
Guideline value derivation	
• allocation to water	20% of upper tolerable intake
• consumption	2 litres/day
Additional comments	<p>It is important that a proper balance be achieved between recommended intakes and undesirable intakes in determining an appropriate guideline value for selenium in drinking-water. While for most parts of the world, the concentration of selenium in drinking-water will not exceed 10 µg/l, there are circumstances in which selenium may be elevated significantly above normal concentrations, and guidance may be required. Where selenium intake from the diet is known, this should be used in determining a concentration that ensures that intake is safe and sufficient. Where selenium intake from the diet is not known, guidance may be required.</p> <p>For most Member States, a drinking-water guideline for selenium is unnecessary. Where there are regions of high intake from a number of sources, of which drinking-water may be one, then Member States should take into consideration exposure from all sources in determining actions to reduce exposure. For drinking-water, this may include using alternative sources, blending low-selenium sources with high-selenium sources as well as considering selenium removal.</p>
Assessment date	2010
Principal references	FAO/WHO (2004) <i>Vitamin and mineral requirements in human nutrition</i> WHO (2011) <i>Selenium in drinking-water</i>

Selenium is an essential element for humans, and there are indications that selenium status may be marginal in many parts of the world, including western Europe. The potential for adverse effects from selenium deficiency appears to be dependent on a number of factors, including overall health and nutritional status. Very low selenium status in humans has been associated with a juvenile, multifocal myocarditis called Keshan disease and a chondrodystrophy called Kaschin-Beck disease. Several studies have also found blood selenium levels to be inversely associated with the prevalence of several types of cancer.

High intakes of selenium are also associated with a number of specific diseases and the potential for adverse effects, but, again, this seems to be strongly influenced by other factors. Symptoms in people with high urinary selenium levels included gastrointestinal disturbances, discoloration of the skin, decayed teeth, hair or nail loss, nail abnormalities and changes in peripheral nerves. Slight biochemical changes have also been observed. One case of selenium toxicity directly attributable to a water source (well water containing selenium at a concentration of 9 mg/l) has been reported. The

average dietary intake that is associated with selenosis has been found to be in excess of 900 µg/day.

As selenium is an essential element, various national and international organizations have established recommended daily intakes of selenium. A joint FAO/WHO consultation recommended intakes of 6–21 µg of selenium per day for infants and children, according to age, 26 and 30 µg of selenium per day for adolescent females and males, respectively, and 26 and 35 µg of selenium per day for adult females and males, respectively.

Because of concern about the adverse effects resulting from exposure to excessive levels of selenium, various national and international organizations have established upper limits of exposure for selenium. FAO/WHO established an upper tolerable limit for selenium of 400 µg/day.

### **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/l. Levels in drinking-water treated with silver for disinfection may be above 50 µg/l. Recent estimates of daily intake are about 7 µg per person.

Reason for not establishing a guideline value	Available data inadequate to permit derivation of health-based guideline value
Assessment date	1993
Principal reference	WHO (2003) <i>Silver in drinking-water</i>

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 experiments with laboratory animals.

The low levels of silver in drinking-water, generally below 5 µg/l, are not relevant to human health with respect to argyria. In contrast, 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/l (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.

### **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/l (2 µg/l)
Occurrence	Frequently detected in groundwater and surface water at concentrations of up to a few micrograms per litre
TDI	0.52 µg/kg body weight, based on a NOAEL of 0.52 mg/kg 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 interspecies and intraspecies variation and 10 for possible non-genotoxic carcinogenicity)
Limit of detection	0.01 µg/l by GC-MS; 0.1–0.2 µg/l by GC with flame thermionic detection
Treatment performance	0.1 µg/l should be achievable using GAC
Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	1993
Principal reference	WHO (2003) <i>Simazine in drinking-water</i>

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 (not classifiable as to its carcinogenicity to humans).

### **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/l, 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.

Reason for not establishing a guideline value	Not of health concern at levels found in drinking-water
Additional comments	May affect acceptability of drinking-water
Assessment date	1993
Principal reference	WHO (2003) <i>Sodium in drinking-water</i>

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/l may give rise to unacceptable taste (see chapter 10).

**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	<i>Sodium dichloroisocyanurate</i> : 50 mg/l (50 000 µg/l) <i>Cyanuric acid</i> : 40 mg/l (40 000 µg/l)
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 body weight for anhydrous sodium dichloroisocyanurate and 1.54 mg/kg body weight for cyanuric acid, based on a NOEL of 154 mg/kg body weight per day (equivalent to 220 mg/kg body weight per day as anhydrous sodium dichloroisocyanurate) for urinary tract and cardiac lesions from a 2-year study of rats exposed to sodium cyanurate and using an uncertainty factor of 100 for interspecies and intraspecies variation
Limit of detection	0.001 mg/l by GC with flame thermionic specific detection; 0.05 mg/l by reversed-phase LC with UV detection; 0.09 mg/l by GC with MS selective ion monitoring
Treatment performance	At very high chlorine doses (up to 10 mg/l), the sodium cyanurate concentration would be below 11 mg/l. 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 value derivation	<ul style="list-style-type: none"> <li>● allocation to water 80% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
Additional comments	<p>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/l for free chlorine.</p> <p>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.</p>

Assessment date	2007
Principal references	FAO/WHO (2004) <i>Evaluation of certain food additives and contaminants</i> WHO (2008) <i>Sodium dichloroisocyanurate in drinking-water</i>

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.

### 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/l (20 µg/l)
Occurrence	Has been detected in drinking-water and surface water at concentrations below 1 µg/l
TDI	7.7 µg/kg body weight, based on a NOAEL of 7.7 mg/kg 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 interspecies and intraspecies variation and 10 for the carcinogenicity and genotoxicity of the reactive intermediate styrene-7,8-oxide)
Limit of detection	0.3 µg/l by GC with photoionization detection and confirmation by MS
Treatment performance	0.02 mg/l may be achievable using GAC
Guideline value derivation	<ul style="list-style-type: none"> <li>• allocation to water 10% of TDI</li> <li>• weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>
Additional comments	May affect the acceptability of drinking-water at the guideline value
Assessment date	1993
Principal reference	WHO (2003) <i>Styrene in drinking-water</i>

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 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 (possibly carcinogenic to humans). 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).

### **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 groundwater 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.

Reason for not establishing a guideline value	Not of health concern at levels found in drinking-water
Additional comments	May affect acceptability of drinking-water
Assessment date	2003
Principal reference	WHO (2003) <i>Sulfate in drinking-water</i>

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 study with piglets and from tap water studies with human volunteers indicate a laxative effect at concentrations of 1000–1200 mg/l, 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/l. The presence of sulfate in drinking-water may also cause noticeable taste (see chapter 10) and may contribute to the corrosion of distribution systems.

### **2,4,5-T**

The half-lives for degradation of chlorophenoxy herbicides, including 2,4,5-T (CAS No. 93-76-5), also known as 2,4,5-trichlorophenoxyacetic acid, in the environment are in the order of several days. Chlorophenoxy herbicides are not often found in food.

## GUIDELINES FOR DRINKING-WATER QUALITY

Guideline value	0.009 mg/l (9 µg/l)
Occurrence	Chlorophenoxy herbicides not frequently found in drinking-water; when detected, concentrations usually no greater than a few micrograms per litre
TDI	3 µg/kg body weight, based on a NOAEL of 3 mg/kg 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 interspecies 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/l by GC with ECD
Treatment performance	1 µg/l should be achievable using GAC
Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	1993
Principal reference	WHO (2003) <i>Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in drinking-water</i>

Chlorophenoxy herbicides, as a group, have been classified in Group 2B (possibly carcinogenic to humans) by IARC. However, the available data from studies in exposed populations and experimental 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.

### **Terbutylazine**

Terbutylazine (CAS No. 5915-41-3), or TBA, a herbicide that belongs to the chlorotriazine family, is used in both pre-emergence 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/l (7 µg/l)
Occurrence	Concentrations in water seldom exceed 0.2 µg/l, although higher concentrations have been observed.
TDI	2.2 µg/kg body weight, based on a NOAEL of 0.22 mg/kg 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 interspecies and intraspecies variation)

## 12. CHEMICAL FACT SHEETS

Limit of detection	0.1 µg/l by HPLC with UV detection
Treatment performance	0.1 µg/l should be achievable using GAC
Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	1998
Principal reference	WHO (2003) <i>Terbutylazine in drinking-water</i>

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.

### ***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/l (40 µg/l)
Occurrence	Concentrations in drinking-water are generally below 3 µg/l, although much higher concentrations have been detected in well water (23 mg/l) and in contaminated groundwater (1 mg/l)
TDI	14 µg/kg 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/l by GC with ECD; 4.1 µg/l by GC-MS
Treatment performance	0.001 mg/l should be achievable using air stripping
Guideline value derivation	
• allocation to water	10% of TDI
• weight	60 kg adult
• consumption	2 litres/day
Assessment date	1993
Principal reference	WHO (2003) <i>Tetrachloroethene in drinking-water</i>

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 (probably carcinogenic to humans). 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.

### **Toluene**

Most toluene (in the form of benzene–toluene–ethylbenzene–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/l (700 µg/l)
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/l); it may also penetrate plastic pipes from contaminated soil
TDI	223 µg/kg body weight, based on a LOAEL of 312 mg/kg body weight per day for marginal hepatotoxic effects observed in a 13-week gavage study in mice, adjusting for daily dosing and using an uncertainty factor of 1000 (100 for interspecies 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/l by GC with FID; 6 µg/l by GC-MS
Treatment performance	0.001 mg/l should be achievable using air stripping
Guideline value 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.
Assessment date	2003
Principal reference	WHO (2003) <i>Toluene in drinking-water</i>

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).

### **Total dissolved solids**

Total dissolved solids (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 originates 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.

Reason for not establishing a guideline value	Not of health concern at levels found in drinking-water
Additional comments	May affect acceptability of drinking-water
Assessment date	1993
Principal reference	WHO (2003) <i>Total dissolved solids in drinking-water</i>

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).

### **Trichloroacetic acid**

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

Guideline value	0.2 mg/l (200 µg/l)
Occurrence	Detected in groundwater and surface water distribution systems in the USA at mean concentrations of 5.3 µg/l (up to a maximum of 80 µg/l) and 16 µg/l (up to a maximum of 174 µg/l), respectively; maximum concentration (200 µg/l) measured in chlorinated water in Australia
TDI	32.5 µg/kg body weight, based on a NOAEL of 32.5 mg/kg 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 interspecies 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/l by GC-MS or GC-ECD

Treatment performance	Concentrations may be reduced by installing or optimizing coagulation to remove precursors or by controlling the pH during chlorination.
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 20% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
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.
Assessment date	2003
Principal reference	WHO (2003) <i>Trichloroacetic acid in drinking-water</i>

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.

### **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/l. General population exposure will primarily result from air and food.

Reason for not establishing a guideline value	Occur in drinking-water at concentrations well below those of health concern, and health-based value would exceed lowest reported odour threshold
Assessment date	2003
Principal reference	WHO (2003) <i>Trichlorobenzenes in drinking-water</i>

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/l can be calculated for total TCBs on the basis of a TDI of 7.7 µg/kg 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 of health concern, it is not considered necessary to derive a formal guideline value. It should be noted that the health-based value exceeds the lowest reported odour threshold in water.

### **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/l; higher concentrations (up to 150 µg/l) have been observed in a few instances. There appears to be increasing exposure to 1,1,1-trichloroethane from other sources.

Reason for not establishing a guideline value	Occur in drinking-water at concentrations well below those of health concern
Assessment date	2003
Principal reference	WHO (2003) <i>1,1,1-Trichloroethane in drinking-water</i>

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/l can be calculated for 1,1,1-trichloroethane on the basis of a TDI of 0.6 mg/kg 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 of health concern, it is not considered necessary to derive a formal guideline value.

### **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/l.

Provisional guideline value	0.02 mg/l (20 µg/l) The guideline value is designated as provisional because of deficiencies in the toxicological database.
Occurrence	Owing to its high volatility, concentrations are normally low (< 1 µg/l) in surface water; concentrations may be higher (usually below 100 µg/l) in groundwater systems where volatilization and biodegradation are limited
TDI	1.46 µg/kg body weight per day in a developmental toxicity study in rats, based on a BMDL <sub>10</sub> (the lower 95% confidence limit corresponding to a 10% increase in extra risk of fetal heart malformations over background) of 0.146 mg/kg body weight per day and using an uncertainty factor of 100 for intraspecies and interspecies variation

## GUIDELINES FOR DRINKING-WATER QUALITY

Limit of detection	0.01–3.0 µg/l by purge-and-trap capillary GC with photoionization detectors or with photoionization detectors and ECD in series; 0.5 µg/l by purge-and-trap capillary GC with MS; 0.01 µg/l by liquid–liquid extraction and GC-ECD; practical quantification limit considered to be achievable by most good laboratories is 5 µg/l
Treatment performance	0.002 mg/l should be achievable by air stripping, possibly in combination with GAC adsorption
Guideline value derivation	<ul style="list-style-type: none"> <li>● allocation to water 50% of TDI</li> <li>● weight 60 kg adult</li> <li>● consumption 2 litres/day</li> </ul>
Additional comments	<p>The guideline value is protective for both cancer and non-cancer end-points.</p> <p>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.</p>
Assessment date	2004
Principal reference	WHO (2005) <i>Trichloroethene in drinking-water</i>

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.

### **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/l (20 µg/l)
Occurrence	Not detected in the small number of drinking-water samples analysed; has been detected in surface water at concentrations above 0.5 µg/l and rarely in groundwater
TDI	7.5 µg/kg body weight, based on a NOAEL of 0.75 mg/kg body weight for mild hepatic effects in a 1-year feeding study in dogs, with an uncertainty factor of 100 (for interspecies and intraspecies variation)
Limit of detection	0.05 µg/l by GC with nitrogen–phosphorus detection



## 12. CHEMICAL FACT SHEETS

Treatment performance	1 µg/l should be achievable using GAC
Guideline value derivation	<ul style="list-style-type: none"> <li>• allocation to water 10% of TDI</li> <li>• weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>
Additional comments	Authorities should note that some impure technical grades of trifluralin could contain potent carcinogenic compounds and therefore should not be used.
Assessment date	1993
Principal reference	WHO (2003) <i>Trifluralin in drinking-water</i>

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 has assigned technical-grade trifluralin to Group 3 (not classifiable as to its carcinogenicity to humans).

### ***Trihalomethanes (bromoform, bromodichloromethane, chloroform, dibromochloromethane)***

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 disinfection by-product 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	<i>Chloroform</i> : 0.3 mg/l (300 µg/l)
	<i>Bromoform</i> : 0.1 mg/l (100 µg/l)
	<i>Dibromochloromethane (DBCM)</i> : 0.1 mg/l (100 µg/l)
	<i>Bromodichloromethane (BDCM)</i> : 0.06 mg/l (60 µg/l)

GUIDELINES FOR DRINKING-WATER QUALITY

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/l; in most circumstances, chloroform is the dominant compound
TDIs	<p><i>Chloroform</i>: 15 µg/kg body weight, derived from the lower 95% confidence limit for 5% incidence of hepatic cysts, generated by physiologically based pharmacokinetic modelling, in 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)</p> <p><i>Bromoform</i>: 17.9 µg/kg 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 intraspecies and interspecies variation and 10 for possible carcinogenicity and short duration of exposure)</p> <p><i>DBCM</i>: 21.4 µg/kg 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 intraspecies 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</p>
Basis of guideline value derivation	<i>BDCM</i> : Application of the linearized multistage model for the observed increases in incidence of kidney tumours in male mice observed in an NTP bioassay
Limit of detection	0.1–0.2 µg/l (method detection limits) by purge-and-trap and liquid–liquid extraction and direct aqueous injection in combination with a chromatographic system; 0.1 µg/l by GC-ECD; 2.2 µg/l by GC-MS
Treatment performance	Concentrations can be reduced by changes to disinfection practice (e.g. reducing organic THM precursors) or using air stripping.
Guideline value derivation	<ul style="list-style-type: none"> <li>• allocation to water 20% of TDI for bromoform and DBCM 75% of TDI for chloroform</li> <li>• weight 60 kg adult</li> <li>• consumption 2 litres/day</li> </ul>
Additional comments on THMs	<p>For authorities wishing to establish a total THM standard to account for additive toxicity, the following fractionation approach could be taken:</p> $\frac{C_{\text{bromoform}}}{GV_{\text{bromoform}}} + \frac{C_{\text{DBCM}}}{GV_{\text{DBCM}}} + \frac{C_{\text{BDCM}}}{GV_{\text{BDCM}}} + \frac{C_{\text{chloroform}}}{GV_{\text{chloroform}}} \leq 1$ <p>where C = concentration and GV = guideline value.</p> <p>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.</p> <p>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.</p>

## 12. CHEMICAL FACT SHEETS

Additional comments on chloroform	<p>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.</p> <p>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.</p>
Additional comments on BDCM	<p>Although a health-based value of 21 µg/l is derived, the previous guideline value of 60 µg/l 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/l may be difficult to achieve using currently available technology without compromising the effectiveness of disinfection.</p> <p>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/l may be difficult to achieve using currently available technology without compromising the effectiveness of disinfection.</p> <p>As BDCM was negative for carcinogenicity in a recent NTP bioassay in which it was dosed in drinking-water, exceedances of the guideline value are not likely to result in an increased risk of cancer.</p>
Assessment date	2004
Principal references	<p>IPCS (2000) <i>Disinfectants and disinfectant by-products</i></p> <p>IPCS (2004) <i>Chloroform</i></p> <p>WHO (2005) <i>Trihalomethanes in drinking-water</i></p>

### 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 mice 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. However, BDCM was negative for carcinogenicity in a recent NTP bioassay in which it was dosed in drinking-water. Exposure to BDCM has also been linked to a possible increase in reproductive effects (increased risk for spontaneous abortion or stillbirth).

### Uranium

Uranium is widespread in nature, occurring in granites and various other mineral deposits. It 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	0.03 mg/l (30 µg/l)
	The guideline value is designated as provisional because of scientific uncertainties surrounding uranium toxicity.
Occurrence	Levels in drinking-water are generally less than 1 µg/l, although concentrations as high as 700 µg/l have been measured in private supplies.
TDI	60 µg, derived from the lower 95% confidence limit on the 95th percentile uranium exposure distribution in a study from Finland, using an uncertainty factor of 10 for intraspecies variation
Limit of detection	0.01 µg/l by ICP-MS; 0.1 µg/l by solid fluorimetry with either laser excitation or UV light; 0.2 µg/l by ICP using adsorption with chelating resin
Treatment performance	1 µg/l should be achievable using conventional treatment (e.g. coagulation or ion exchange)

Guideline value derivation	
• consumption	2 litres/day
Additional comments	Where supplies exceed 30 µg/l, it is important that precipitate action be avoided. Consideration should first be given to exposure from all sources and the availability of alternative safe sources.
	Only chemical, not radiological, aspects of uranium toxicity have been addressed here; for radiological aspects, see chapter 9.
Assessment date	2003, revised in 2011
Principal reference	WHO (2011) <i>Uranium in drinking-water</i>

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  $\beta$ -microglobulin in urine along with modest alterations in proximal tubular function. However, the actual measurements were still within the normal physiological range, and these findings are not consistent between studies.

No clear no-effect concentration has emerged from the human studies to date. This is not surprising, as most of the study populations are quite small, and there is substantial normal variation in the measured parameters in the human population. However, the overall indications are that there is no clear evidence of effects below an exposure concentration of 30 µg/l. In fact, the evidence for effects on the kidney, which appears to be the most sensitive organ, is equivocal until much higher exposure concentrations.

The provisional guideline value of 30 µg/l, which is derived from new epidemiological studies on populations exposed to high uranium concentrations, replaces the previous value derived from experimental animal studies and designated as provisional on the basis of uncertainties regarding the toxicology and epidemiology of uranium as well as difficulties concerning its technical achievability in smaller supplies. It is noted that studies on human populations, when available and of good quality, are the preferred source of health-related information to be used in deriving guideline values.

### **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.

## GUIDELINES FOR DRINKING-WATER QUALITY

Guideline value	0.0003 mg/l (0.3 µg/l)
Occurrence	Rarely detected in surface waters, the concentrations measured generally not exceeding 10 µg/l; much higher concentrations found in groundwater and well water in contaminated areas; concentrations up to 10 µg/l detected in drinking-water
Basis of guideline value 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 <sup>-5</sup> and assuming a doubling of the risk for exposure from birth
Limit of detection	0.01 µg/l by GC-ECD or GC-FID with MS for confirmation
Treatment performance	0.001 mg/l should be achievable using air stripping
Additional comments	<p>The results of the linear extrapolation are nearly identical to those derived using the linearized multistage model.</p> <p>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.</p> <p>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.</p>
Assessment date	2003
Principal references	<p>IPCS (1999) <i>Vinyl chloride</i></p> <p>WHO (2003) <i>Vinyl chloride in drinking-water</i></p>

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 (carcinogenic to humans). Studies of workers employed in the vinyl chloride industry showed a marked exposure–response for all liver cancers, angiosarcomas and hepatocellular carcinoma, but no strong relationship between cumulative vinyl chloride exposure and other cancers. Experimental 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.

### **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.

## 12. CHEMICAL FACT SHEETS

Guideline value	0.5 mg/l (500 µg/l)
Occurrence	Concentrations of up to 8 µg/l 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 body weight, based on a NOAEL of 250 mg/kg body weight per day for decreased body weight in a 103-week gavage study in rats, adjusting for daily dosing and using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for the limited toxicological end-points)
Limit of detection	0.1 µg/l by GC-MS; 1 µg/l by GC-FID
Treatment performance	0.005 mg/l should be achievable using GAC or air stripping
Guideline value 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.
Assessment date	1993
Principal reference	WHO (2003) <i>Xylenes in drinking-water</i>

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 carcinogenicity studies have shown no evidence for carcinogenicity. In vitro as well as in vivo mutagenicity tests have proved negative.

### 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/l, respectively, concentrations in tap water can be much higher as a result of dissolution of zinc from pipes.

Reason for not establishing a guideline value	Not of health concern at levels found in drinking-water
Additional comments	May affect acceptability of drinking-water
Assessment date	1993
Principal reference	WHO (2003) <i>Zinc in drinking-water</i>

In 1982, JECFA proposed a PMTDI for zinc of 1 mg/kg 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 formal guideline value is not required at this time. However, drinking-water containing zinc at levels above 3 mg/l may not be acceptable to consumers (see chapter 10).

## 12.2 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 domestic 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.

### *Bacillus thuringiensis israelensis*

Two *Bacillus thuringiensis israelensis* (Bti) (strain AM65-52) products (water-dispersible granule and ready-to-use tablet) have been evaluated by WHOPES and recommended as mosquito larvicides, including their use against container-breeding mosquitoes. Quality control specifications and efficacy evaluations for Bti water-dispersible granule have been published. WHO recommendations on the use of pesticides in public health are valid only if linked to WHO specifications for their quality control.

Reason for not establishing a guideline value	Not considered appropriate to set guideline values for pesticides used for vector control in drinking-water
Assessment date	2009
Principal references	<p>IPCS (1999) <i>Bacillus thuringiensis</i></p> <p>WHO (2004) <i>Report of the seventh WHOPES working group meeting</i></p> <p>WHO (2006) <i>Report of the ninth WHOPES working group meeting</i></p> <p>WHO (2007) <i>WHO specifications and evaluations for public health pesticides</i></p> <p>WHO (2009) <i>Bacillus thuringiensis israelensis (Bti) in drinking-water</i></p>

Preparations of Bti are widely used against mosquitoes, chironomids and black-flies, and this specific activity against disease vector species has resulted in the use of



Bti in water. Bti is recommended under WHOPES for use in vector control, including against container-breeding mosquitoes, and can be used in drinking-water that will receive little or no further treatment for control of *Aedes aegypti*. It is essential that Bti for larvicidal use be prepared under carefully controlled conditions and properly assayed before use for evidence of potency, for excessive levels of expressed Bti constituents or metabolites that are toxic and for contamination by other undesirable microbes.

Bti itself is not considered to pose a hazard to humans through drinking-water. Therefore, it is not considered necessary or appropriate to establish a health-based value for its use for controlling vector larvae in drinking-water. However, it is vital that authorities can be assured that Bti has been prepared to the highest quality and hygienic standards under appropriate conditions that will meet the WHOPES specifications. It is important that the possible risks are set against the risks from vector-borne diseases such as dengue fever.

Application should be carried out by trained applicators and Bti used in conjunction with other approaches to vector control, including exclusion of mosquitoes from containers and other control options.

### **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/l under WHOPES.

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.

Reason for not establishing a guideline value	Not considered appropriate to set guideline values for pesticides used for vector control in drinking-water
Assessment date	2007
Principal references	FAO/WHO (2002) <i>Pesticide residues in food—2001 evaluations</i> WHO (2008) <i>Diflubenzuron in drinking-water</i>

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 0–0.02 mg/kg body weight. The maximum dosage in drinking-water of 0.25 mg/l would be equivalent to approximately 40% of the upper limit 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 upper limit of 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 upper limit of 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.

### **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/l under WHOPES.

Reason for not establishing a guideline value	Not considered appropriate to set guideline values for pesticides used for vector control in drinking-water
Assessment date	2007
Principal references	FAO/WHO (2002) <i>Pesticide residues in food—2001 evaluations</i> WHO (2008) <i>Methoprene in drinking-water</i>

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 body weight to correct for the purity of the racemate tested. The basis for the ADI was the NOAEL of 500 mg/kg diet, equivalent to 8.6 mg/kg 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 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/l would be equivalent to approximately 66% of the upper limit of the ADI (0.033 mg/kg 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 body weight, and for a 5 kg bottle-fed infant, the exposure

would be approximately 0.15 mg/kg body weight, compared with the upper limit of the ADI of 0.05 mg/kg body weight. However, the low solubility and the high log octanol–water partition coefficient 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.

### **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/l under WHOPES.

Reason for not establishing a guideline value	Not considered appropriate to set guideline values for pesticides used for vector control in drinking-water
Assessment date	2007
Principal references	FAO/WHO (2006) <i>Pesticide residues in food—2005 evaluations</i> WHO (2008) <i>Novaluron in drinking-water</i> .

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 body weight on the basis of the NOAEL of 1.1 mg/kg body weight per day for erythrocyte damage and secondary splenic and liver changes in a 2-year dietary study in rats, using 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/l, the intake of a 60 kg adult drinking 2 litres of water would represent only 17% of the upper limit of the ADI. Similarly, the intake for a 10 kg child drinking 1 litre of water would be 50% of the upper limit of the ADI, whereas a 5 kg bottle-fed infant drinking 0.75 litre of water would receive an intake of 75% of the upper limit of the ADI.

The high log octanol–water partition coefficient 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.

**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.

Reason for not establishing a guideline value	Not recommended for direct addition to drinking-water as part of WHO's policy to exclude the use of any pyrethroids for larviciding of mosquito vectors of human disease
Assessment date	2011
Principal references	FAO/WHO (2000) <i>Pesticide residues in food—1999 evaluations</i> WHO (2011) <i>Permethrin in drinking-water</i>

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 experimental animal studies. Permethrin is not genotoxic. JMPR concluded that technical-grade permethrin is not a reproductive or developmental toxin.

For guidance purposes, a health-based value can be derived from an ADI of 0–0.05 mg/kg body weight, established for technical-grade permethrin with *cis:trans* ratios of 25:75 to 40:60 on the basis of a NOAEL of 5 mg/kg body weight per day in a 2-year dietary study in rats, which was based on clinical signs and changes in body and organ weights and blood chemistry at the next higher dose, and a NOAEL of 5 mg/kg body weight per day in a 1-year study in dogs, based on reduced body weight at 100 mg/kg body weight per day, and applying an uncertainty factor of 100 for interspecies and intraspecies variation. Assuming a 60 kg adult drinking 2 litres of water per day and allocating 20% of the upper limit of the ADI to drinking-water, a health-based value of 0.3 mg/l can be derived.

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.

**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/l to water.

## 12. CHEMICAL FACT SHEETS

Reason for not establishing a guideline value	Not recommended for direct application to drinking-water unless no other effective and safe treatments are available
Assessment date	2007
Principal references	FAO/WHO (1993) <i>Pesticide residues in food—1992 evaluations</i> FAO/WHO (2008) <i>Pesticide residues in food—2006 evaluations</i> WHO (2008) <i>Pirimiphos-methyl in drinking-water</i>

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 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 body weight per day (the highest dose tested). On this basis, JMPR revised the ADI to 0–0.03 mg/kg 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/l, a 60 kg adult drinking 2 litres of water would have an intake of 0.033 mg/kg body weight, compared with the upper limit of the ADI of 0.03 mg/kg body weight. The intake for a 10 kg child drinking 1 litre of water would be 0.1 mg/kg body weight; for a 5 kg bottle-fed infant drinking 0.75 litre, it would be 0.15 mg/kg body weight. There is uncertainty regarding the level that would cause effects in humans, as 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 acute reference dose of 0.2 mg/kg 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 octanol–water partition coefficient of pirimiphos-methyl indicate that the larvicide 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.

### **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/l under WHOPES.

Reason for not establishing a guideline value	Not considered appropriate to set guideline values for pesticides used for vector control in drinking-water
Assessment date	2007
Principal references	FAO/WHO (2000) <i>Pesticide residues in food—1999 evaluations</i> WHO (2010) <i>Pyriproxyfen in drinking-water</i>

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 body weight on the basis of an overall NOAEL of 10 mg/kg 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 using 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/l would be equivalent to less than 1% of the upper limit 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 upper limit of 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 upper limit of the ADI. The low solubility and the high log octanol–water partition coefficient 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.

### **Spinosad**

Spinosad is a natural product derived from the bacterium *Saccharopolyspora spinosa*. Spinosad DT is a mixture of spinosyn A and spinosyn D. It is used for mosquito control in potable water in containers.

Spinosad DT 7.48% is specified for use as a vector control agent in drinking-water sources against *Aedes aegypti* by WHO under WHOPES. Formulations for control of vectors are specified by WHO at a dose of 0.25–0.5 mg/l. The expected duration of efficacy under field conditions is 4–6 weeks.

Three formulations of spinosad have been evaluated by WHOPES for mosquito larviciding. WHO specifications for quality control and international trade have been published for the three formulations: i.e. spinosad granules (636/GR), aqueous suspension concentrate (636/SC) and tablets for direct application (636/DT). Only the tablet formulation is used for mosquito larviciding in potable water at the dosage of 0.25–0.5 mg/l of the active ingredient.

In a 14-day study conducted by the manufacturer, a single tablet was added to a 200-litre container of water, and 10% of the water in this container was replenished each day of the study. The concentration of spinosad was found to be in the range 26.5–51.7 µg/l.

Reason for not establishing a guideline value	Not considered appropriate to set guideline values for pesticides used for vector control in drinking-water
Assessment date	2009
Principal references	FAO/WHO (2002) <i>Pesticide residues in food—2001 evaluations</i> WHO (2010) <i>Spinosad in drinking-water</i>

It is not appropriate to set a formal guideline value for spinosad DT for use to control vectors breeding in drinking-water containers; however, it is appropriate to compare the probable intakes with the ADI of 0–0.02 mg/kg body weight, with no acute reference dose set because of its low acute toxicity. The maximum concentration actually achieved with the slow-release formulation was approximately 52 µg/l. The intake would therefore be:

- 39 µg for a 5 kg bottle-fed infant assuming consumption of 0.75 litre = 7.8 µg/kg body weight
- 52 µg for a 10 kg child assuming consumption of 1 litre = 5.2 µg/kg body weight
- 104 µg for a 60 kg adult assuming consumption of 2 litres = 1.7 µg/kg body weight.

However, this could be higher if drinking-water consumption is also higher.

This means that the exposure is well below the upper limit of the ADI for all sectors of the population. Even the application of a double dose would result in exposure below the upper limit of the ADI.

The ADI is, of course, set for lifetime exposure, and the average exposure over time will be lower than the exposures indicated above.

### **Temephos**

Temephos is an organophosphorus insecticide that is used mainly as a larvicide to control mosquitoes on ponds, marshes and swamps and midges, black flies and other insects in public health. It is also used for mosquito control in potable water in containers. It is specified for use as a vector control agent in drinking-water sources by WHO under WHOPES. Formulations for control of vectors are specified by WHO, and only those approved by WHOPES should be used for this purpose. The recommendation for the use of temephos in potable water is that the dosage should not exceed 1 mg/l.

Reason for not establishing a guideline value	Not considered appropriate to set guideline values for pesticides used for vector control in drinking-water
Assessment date	2009
Principal references	FAO/WHO (2008) <i>Pesticide residues in food—2006 evaluations</i> WHO (2009) <i>Temephos in drinking-water</i>

The NOAEL for human risk assessment for temephos is 2.3 mg/kg body weight per day on the basis of inhibition of brain acetylcholinesterase activity in rats, as determined by JMPR in 2006. Although JMPR considered that the database was

insufficiently robust to serve as the basis for establishing an ADI, for the purposes of these Guidelines, a TDI of 0.023 mg/kg body weight can be calculated from this NOAEL, using an uncertainty factor of 100. Young animals do not appear to be significantly more sensitive than adults, and exposure from food is considered to be low.

It is not appropriate to set a formal guideline value for temephos used as a vector control agent in drinking-water. Where temephos is used for vector control in potable water, this will involve less than lifetime exposure. The maximum dosage in drinking-water of 1 mg/l for a 60 kg adult drinking 2 litres of water per day would be equivalent to approximately 0.033 mg/kg body weight, compared with the TDI of 0.023 mg/kg body weight. The exposure for a 10 kg child drinking 1 litre of water would be approximately 0.1 mg/kg body weight; for a 5 kg bottle-fed infant, the exposure would be approximately 0.15 mg/kg body weight, compared with the TDI of 0.023 mg/kg body weight.

Consideration should be given to using alternative sources of water for small children and bottle-fed infants for a period after an application of temephos, where this is practical.

However, exceeding the TDI does not necessarily mean that this will result in adverse effects. Indeed, the low solubility and the high log octanol–water partition coefficient of temephos indicate that it is unlikely to remain in solution at the maximum recommended applied dose, and the use of the slow-release formulation should result in very much lower concentrations than the approved dose of 1 mg/l and actual exposures much lower than the theoretical exposures calculated above.