WHO/SDE/WSH/03.04/10
English only

Mercury in Drinking-water

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

Originally published in **Guidelines for drinking-water quality**, 2nd ed. Vol. 2. *Health criteria and other supporting information.* World Health Organization, Geneva, 1996.

Preface

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

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

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

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

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

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

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

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

Acknowledgements

The work of the following coordinators was crucial in the development of this background document for development of WHO *Guidelines for drinking-water quality*:

J.K. Fawell, Water Research Centre, United Kingdom
(inorganic constituents)
U. Lund, Water Quality Institute, Denmark
(organic constituents and pesticides)
B. Mintz, Environmental Protection Agency, USA
(disinfectants and disinfectant by-products)

The WHO coordinators were as follows:

Headquarters:
H. Galal-Gorchev, International Programme on Chemical Safety
R. Helmer, Division of Environmental Health

Regional Office for Europe:
X. Bonnefoy, Environment and Health
O. Espinoza, Environment and Health

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

The efforts of all who helped in the preparation and finalization of this document, including those who drafted and peer reviewed drafts, are gratefully acknowledged.

The convening of the experts meetings was made possible by the financial support afforded to WHO by the Danish International Development Agency (DANIDA), Norwegian Agency for Development Cooperation (NORAD), the United Kingdom Overseas Development Administration (ODA) and the Water Services Association in the United Kingdom, the Swedish International Development Authority (SIDA), and the following sponsoring countries: Belgium, Canada, France, Italy, Japan, Netherlands, United Kingdom of Great Britain and Northern Ireland and United States of America.

GENERAL DESCRIPTION

Physicochemical properties

Property	*Value*
Physical state	Dense, silver-white metal; liquid at normal temperatures and pressures
Vapour pressure	0.16 Pa at 20 °C
Stability	Carbon–mercury bond in organic mercury compounds is chemically stable

Major uses

Mercury is used for the cathode in the electrolytic production of chlorine and caustic soda, in electrical appliances (lamps, arc rectifiers, mercury cells), in industrial and control instruments (switches, thermometers, barometers), in laboratory apparatus, in dental amalgams, and as a raw material for various mercury compounds. The latter are used as fungicides, antiseptics, preservatives, pharmaceuticals, electrodes, and reagents.

Environmental fate

The solubility of mercury compounds in water varies: elemental mercury vapour is insoluble, mercury(II) chloride is readily soluble, mercury(I) chloride much less soluble, and mercury sulfide has a very low solubility.

Methylation of inorganic mercury has been shown to occur in columns of fresh water and in seawater (*1*), and bacteria (*Pseudomonas* spp.) isolated from mucous material on the surface of fish and soil were able to methylate mercury under aerobic conditions. Some anaerobic bacteria that possess methane synthetase are also capable of mercury methylation (*2*). Once methylmercury [the generic term "methylmercury" is used throughout this text to refer to monomethylmercury compounds] is released from microbes, it enters the food chain as a consequence of rapid diffusion and tight binding to proteins in aquatic biota. The enzymology of CH_3Hg^+ hydrolysis and mercury(II) ion reduction is now understood in some detail. Environmental levels of methylmercury depend on the balance between bacterial methylation and demethylation (*3*).

ANALYTICAL METHODS

Inorganic mercury is determined by flameless atomic absorption spectrometry (*4*). Cold vapour atomic absorption spectrometry and atomic fluorescence spectrometry have detection limits of 50 and 1 ng/litre, respectively.

Gas chromatography is commonly used for the determination of alkylmercury compounds. The neutron activation procedure is regarded as the most accurate and is generally used as the reference method (*3*).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

Mercury levels in air are in the range 2–10 ng/m^3.

Water

- Inorganic mercury

Levels of mercury in rainwater are in the range 5–100 ng/litre, but mean levels as low as 1 ng/litre have been reported (*3*). Naturally occurring levels of mercury in groundwater and surface water are less than 0.5 µg/litre, although local mineral deposits may produce higher levels in groundwater. In 16 groundwaters and 16 shallow wells surveyed in the USA, mercury levels exceeded the maximum contaminant level of 2 µg/litre set by the US Environmental Protection Agency for drinking-water (*5*). An increase in the mercury concentration up to 5.5 µg/litre was reported for wells in Izu Oshima Island (Japan), where volcanic activity is frequent (*6*). The concentration range for mercury in drinking-water is the same as in rain, with an average of about 25 ng/litre (*3*).

- Organic mercury

In a contaminated lake system in Canada, methylmercury was found to constitute a varying proportion of total mercury, depending on the lake (*3*). There have been no reports of methylmercury in drinking-water.

Food

Food is the main source of mercury in non-occupationally exposed populations. Fish and fish products account for most of the organic mercury in food. The average daily intake of mercury from food is in the range 2–20 µg/day, but may be much higher in regions where ambient waters have become contaminated with mercury and where fish constitute a high proportion of the diet (*7*).

Estimated total exposure and relative contribution of drinking-water

On the assumption of an ambient air level of 10 ng/m^3, the average daily intake of inorganic mercury by inhalation would amount to about 0.2 µg. If a level in drinking-water of 0.5 µg/litre is assumed, the average daily intake of inorganic mercury from this source would amount to about 1 µg. The average daily intake of mercury from food is in the range 2–20 µg/day.

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

- Inorganic mercury

About 7–8% of ingested mercury in food is absorbed; absorption from water may be 15% or less, depending on the compound. About 80% of inhaled metallic mercury vapour is retained by the body, whereas liquid metallic mercury is poorly absorbed via the gastrointestinal tract. Inhaled aerosols of inorganic mercury are deposited in the respiratory tract and absorbed to an extent depending on particle size (*8*).

Inorganic mercury compounds are rapidly accumulated in the kidney, the main target organ for these compounds. The biological half-time is very long, probably years, in both animals and humans. Mercury salts are excreted via the kidney, liver, intestinal mucosa, sweat glands, salivary glands, and milk; the most important routes are via the urine and faeces (*8*).

- Organic mercury

Dimethylmercury is almost completely absorbed through the gastrointestinal tract; after absorption it rapidly appears in the blood, where, in humans, 80–90% is bound to red cells. Demethylation of methylmercury to inorganic mercury occurs at a slow but significant rate. The greater intrinsic toxicity of methylmercury as compared with inorganic mercury is due to its lipid solubility, which enables it to cross biological membranes more easily, and especially to enter the brain, spinal cord, and peripheral nerves, and to cross the placenta (*3*).

Most methylmercury is excreted in the inorganic form. The site and mechanism of demethylation are still not well understood (*3*).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

- Inorganic mercury

Short-term exposure

The toxic effects of inorganic mercury compounds are mainly in the kidney. Lesions in the proximal tubular cells were detected after a single intraperitoneal injection of 1 μmol of mercury(II) chloride per kg of body weight (0.2 mg/kg of body weight as mercury) in male rats. Accumulation of mercury in the kidneys, however, indicated that the absorption efficiency was much greater than that expected from the gastrointestinal tract (*9*).

When rats were given mercury(II) chloride (3 mg/kg of body weight) by gavage twice a week for 60 days, examination by immunofluorescence showed that deposits for IgG were present in the renal glomeruli. Morphological lesions of the ileum and colon were also observed, with abnormal deposits of IgA in the basement membranes of the intestinal glands and of IgG in the basement membranes of the lamina propria (*10*).

When rats were exposed to mercury(II) chloride (1 mg/kg of body weight per day) by incubation or subcutaneous injection for up to 11 weeks, the rate of body weight gain decreased after 20 days, and actual weight loss occurred after 65–70 days. There were also neuropathological effects, first detected after 2 weeks, namely peripheral vacuolization of cells in the dorsal root ganglia, followed by the development of multiple small lesions in the ganglia (*11*).

A single dose of 1 mg/kg of body weight of mercury(II) chloride or methylmercury(II) chloride, either orally or by subcutaneous injection, resulted in leakage of dye into the nervous parenchyma within 12 h, indicating that these compounds can increase the permeability of the blood–brain barrier (*11*).

Long-term exposure

Rats injected subcutaneously 3 times weekly for up to 8 months with doses of inorganic mercury ranging from 0.05 to 2.5 mg/kg of body weight per injection (0.02–1.07 mg/kg of body weight per day) developed renal damage. This was characterized by an initial production of antiglomerular basement membrane antibodies, followed by the appearance of immune complex deposits in the glomerular tufts and small renal arteries accompanied by proteinuria and hypoalbuminaemia (*12*).

Reproductive toxicity, embryotoxicity, and teratogenicity

Controlled mating tests in which male mice were injected with single doses of mercury(II) chloride (1 mg of mercury per kg of body weight) showed a significant decrease in fertility as compared with controls (*13*). Normal fertility was restored after about 2 months.

Gradual changes in testicular tissues were noted in rats treated with mercury(II) chloride at doses of 0.05 or 0.1 mg/kg of body weight intraperitoneally over 90 days (*14*). There was a decrease in seminiferous tubule diameter, spermatogenic cell counts, and Leydig's cell nuclear diameter as compared with controls.

Of female hamsters given a total of 3–4 mg of mercuric chloride during the first estrous cycle, 60% did not ovulate by day 1 of the third cycle (*15*). Ovulation was inhibited in female hamsters injected with mercury(II) chloride at high doses (6.4 or 12.8 mg of mercury per kg of body weight) during day 1 of the estrous cycle (*16*). Female hamsters injected with 1 mg of mercury(II) chloride per day during one estrous cycle exhibited significantly higher levels of follicle-stimulating hormone in their pituitaries as compared with controls (*17*).

Pregnant Wistar rats were exposed intravenously to mercury(II) chloride on different days of gestation. At mid-gestation, the minimum effective teratogenic dose of mercury (0.79 mg/kg of body weight) was high in relation to the maternal LD_{50}, and the incidence of fetal malformations, mainly brain defects, was 23% in all live fetuses. In rats of different gestational ages, uptake of Hg^{2+} by the fetuses at this dose level decreased sharply between days 12 and 13 (*18*).

- Organic mercury

Short-term exposure

In rats fed methylmercury dicyandiamide 5 days per week for 59 days, extensive damage to the renal cortex occurred with extensive inflammatory reaction surrounding the tubules and some early fibrosis even at the lowest dose of 0.6 mg/kg of body weight per day (*19*). Tubular degeneration of the kidney was also evident after subcutaneous injection of 10 mg/kg of body weight per day into rats for 7 consecutive days (*20*). In contrast to the effects of high doses of methylmercury on rats, kidney damage was not reported in cats exposed to 0.45 mg/kg of body weight (*21*) or in monkeys exposed to either 0.05 mg/kg of body weight per day (*22*) or to doses resulting in blood levels of up to 4 µg of mercury per ml of blood (*23*).

In cats, convulsions occurred after 60–83 days of exposure to 0.45 mg of methylmercury per kg of body weight per day; they were preceded 4–11 days earlier by progressive behavioural changes. Kittens were fed commercially available tuna contaminated with 0.3–0.5 mg of methylmercury(II) chloride per kg for 11 months. The total mercury intake over the period averaged 6.3 mg per cat or about 19 µg/day. Neurological disturbances were observed in three kittens after 7–11 months (*24*).

Squirrel monkeys were exposed for periods of up to 35 days to repeated oral doses of methylmercury(II) nitrate mixed in the food or by stomach tube. The threshold for both behavioural and central nervous system pathology occurred at blood mercury concentrations in the range 0.75–1.2 mg/litre (*25*).

Long-term exposure

In a study in which cats were fed methylmercury(II) chloride in a fish diet at doses of 0.003, 0.008, 0.020, 0.046, 0.074, or 0.176 mg/kg of body weight per day, 7 days a week for 2 years, detectable neurological impairment occurred in the group given 0.046 mg/kg of body weight

per day after 60 weeks; this concentration was the lowest at which such impairment occurred. Pathological changes in the nervous system were restricted to the brain and dorsal root ganglia and were not seen at doses below 0.074 mg/kg of body weight per day (*26*).

Stumptail, pigtail, and squirrel monkeys were given methylmercury(II) chloride in food for periods in excess of 1000 days. This dosage regime was designed to maintain the blood mercury level at 1–4 mg/litre of blood. The critical effects seen were reduced sensitivity to visual stimuli at low luminescence and tremor on reaching for a small object. All monkeys with a blood concentration above 2 mg/litre developed symptoms with latent periods ranging from less than 20 to 200 days (*23*).

Cynomolgus monkeys were fed methylmercury from birth at doses of 0.05 mg/kg of body weight per day for 3–4 years. Blood concentrations of mercury peaked at 1.2–1.4 mg/litre, then declined after weaning to a steady level of 0.6–0.9 mg/litre. No overt signs of toxicity were noted but, when tested after 3–4 years, the monkeys exhibited impaired spatial vision under conditions of both high and low luminescence (*22*).

Reproductive toxicity, embryotoxicity, and teratogenicity

Mice were given single doses of 3.6, 5.3, 8, 12, 18, or 27 mg of methylmercury(II) chloride per kg of body weight at 9.5, 12.5, or 15.5 days post-fertilization (*27*). The trend among F_1 females towards an adverse effect of dose on litter size, although not statistically significant, was in the direction to be expected if methylmercury(II) chloride can affect oogenesis in females exposed during fetal life.

A single dose of 2, 3, or 4 mg of mercury(II) ethanoate (about 1.3–2.5 mg of mercury) was injected intravenously in three groups of female hamsters on day 8 of gestation (*28*). The exposed groups showed resorption frequencies of 12, 34, and 52%, respectively, as compared with 4% in the controls.

High doses of methylmercury given to pregnant rodents produced cleft palate (*29,30*). Prenatal exposure of rats can produce renal functional abnormalities detectable in offspring at 42 days of age (*31*).

Female rats were injected with 0, 6, or 10 mg of methylmercury(II) chloride per kg of body weight on gestational days 6–9 (*32*). Dams given 10 mg/kg of body weight either failed to give birth or the young were stillborn. External morphology was normal for rats given either of the two lower doses. Methylmercury produced hydrocephalus, decreased thickness of the cerebral cortex in the parietal section, and increased thickness of the hippocampus in the occipital section; with these exceptions, the brains of mercury-treated rats showed normal development.

Hamsters were given either 10 mg of methylmercury per kg of body weight on gestational day 10 or 2 mg/kg on gestational days 10–15 (*33,34*). In the neonatal cerebellar cortex, degenerative changes such as accumulation of lysosomes and areas of floccular cytoplasmic degradation were frequently observed in the neuroblast granular layer as well as in more differentiated neural elements in the molecular and internal granular layers. Pyknotic nuclei were seen singly and in groups throughout the external granular layer of treated animals. In the adult cerebellum, focal areas of astrogliosis were observed in the molecular layer of treated animals.

Mutagenicity and related end-points

Animal and cell culture studies confirm that methylmercury damages chromosomes if given orally at a dose of 5 mg/kg of body weight to pregnant mice (*16,35*), intraperitoneally at 2

mg/kg of body weight daily for 3 weeks to adult hamsters (*36*), and intraperitoneally at 10 mg/kg of body weight to ovulating Syrian hamsters (*37*). Methylmercury at low concentrations (0.05–0.1 μmol/litre) has been reported to interfere with gene expression in *in vitro* cultures of glioma cells (*38*). Non-disjunction and sex-linked recessive lethal mutations were induced in *Drosophila melanogaster* by treatment with methylmercury (*39*).

Carcinogenicity

Groups of mice were fed 15 or 30 mg of methylmercury per kg of diet for up to 78 weeks. The majority of the 30 mg/kg group died from neurotoxicity by week 26. Histopathological examination of kidney tissue from all animals surviving after 53 weeks revealed renal tumours in 13 of 16 males in the 15 mg/kg group. Of these, 11 were classified as adenocarcinomas and two as adenomas (*40*).

EFFECTS ON HUMANS

- Inorganic mercury

Acute exposure

Mercury will cause severe disruption of any tissue with which it comes into contact in sufficient concentration, but the two main effects of mercury poisoning are neurological and renal disturbances. The former is characteristic of poisoning by methyl- and ethylmercury(II) salts, in which liver and renal damage are of relatively little significance, the latter of poisoning by inorganic mercury.

In general, however, the ingestion of acute lethal toxic doses of any form of mercury will result in the same terminal signs and symptoms, namely shock, cardiovascular collapse, acute renal failure, and severe gastrointestinal damage. Acute oral poisoning results primarily in haemorrhagic gastritis and colitis; the ultimate damage is to the kidney. Clinical symptoms of acute intoxication include pharyngitis, dysphagia, abdominal pain, nausea and vomiting, bloody diarrhoea, and shock. Later, swelling of the salivary glands, stomatitis, loosening of the teeth, nephritis, anuria, and hepatitis occur (*41*).

Ingestion of 500 mg of mercury(II) chloride causes severe poisoning and sometimes death in humans (*42*). Acute effects result from the inhalation of air containing mercury vapour at concentrations in the range of 0.05–0.35 mg/m^3 (*43,44*). Exposure for a few hours to 1–3 mg/m^3 may give rise to pulmonary irritation and destruction of lung tissue and occasionally to central nervous system disorders (*45*).

Dermal exposure to alkyl mercurials may give rise to acute toxic dermatitis and eczematous changes.

Long-term exposure

Many studies involving the observation of more than 1000 individuals indicate that the classical signs and symptoms of elemental mercury vapour poisoning (objective tremors, mental disturbances, and gingivitis) may be expected to appear after chronic exposure to air mercury concentrations above 0.1 mg/m^3 (*8*). Nonspecific neurological and physiological symptoms were also associated with lower exposure levels.

Considerable mercury exposure of children of workers at a thermometer plant has been reported (*46*). The median urine mercury level of 23 such children was 25 μg/litre as compared with 5 μg/litre in 39 controls. No signs of mercury intoxication were seen on clinical examination or reported by parents (*3*).

- Organic mercury

The adverse health effects of occupational exposure to alkylmercury compounds constitute what is known as the Hunter-Russel syndrome (concentric constriction of the visual field, ataxia, dysarthria, etc.); this was seen in four workers exposed to methylmercury fungicide (*47*).

Methyl- and ethylmercury compounds have been the cause of the largest number of cases of mercury poisoning and of fatalities in the general population as a result of the consumption of contaminated fish or of bread prepared from cereals treated with alkylmercury fungicides. The earliest effects are nonspecific, e.g. paraesthesia, malaise, and blurred vision. These are followed by concentric constriction of the visual field, deafness, dysarthria, and ataxia. In the worst cases, the patient may go into coma and ultimately die. At high doses, methylmercury affects the peripheral nervous system in human subjects (*48*).

The two major epidemics of methylmercury poisoning in Japan, in Minamata Bay and in Niigata, both known as Minamata disease, were caused by the industrial release of methylmercury and other mercury compounds into Minamata Bay and into the Agano River, followed by accumulation of the mercury in edible fish. The maximum blood level of methylmercury without adverse health effects was estimated to be 0.33 μg/ml based on the epidemiological study of the Minamata disease endemic area (*49*). By 1971, a total of 269 cases of Minamata disease had been reported in Minamata and Niigata, of which 55 proved fatal. By March 1989, 2217 cases of Minamata disease had been officially recognized in Minamata and 911 cases in Niigata (*50*).

The largest recorded epidemic caused by the ingestion of contaminated bread prepared from wheat and other cereals treated with alkyl (methyl- or ethyl-) mercury fungicides took place in the winter of 1971–72 in Iraq, and resulted in the admission of over 6000 patients to hospital and over 500 deaths (*51*). Previous epidemics have occurred in Guatemala, Iraq, and Pakistan, and on a limited scale in other countries (*3,8,52*).

The Cree Indians of northern Quebec were also known to be exposed to methylmercury through the consumption of contaminated local fish. The relationship between measures of exposure and neurological abnormalities was studied in two communities. A positive association was found between neurological abnormalities and methylmercury exposure in both communities, but the relationship was statistically significant only in one of them (*53,54*).

The first indication of possible congenital Minamata disease was the unusual occurrence of cerebral palsy-like conditions in nine infants in the endemic areas (population about 1700) during 21 months. These infants had severe cerebral involvement (palsy and mental retardation); mild or no symptoms of poisoning were seen in their mothers, although there is a possibility that slight symptoms might have been overlooked (*3*).

According to an epidemiological study of an outbreak in Iraq, the clinical picture was dose-dependent. In those who were exposed to high maternal blood levels of methylmercury, the picture was one of cerebral palsy indistinguishable from that resulting from other causes (microcephaly, hyper-reflexia, and gross motor and mental impairment, associated with blindness or deafness). Milder forms were not easy to diagnose during the first few months of life, but became clearer with time. The cases showed mainly psychomotor impairment and persistence of pathological reflexes (*53,55–57*). The relationship between prenatal exposure to methylmercury and neurological and developmental abnormalities was also studied. Abnormality of the tendon reflex was positively associated with methylmercury exposure

only in boys, without a dose–response relationship (*58*). Findings in the milder cases were quite similar to those associated with the minimal brain syndrome (*3*).

Marsh et al. (*59*) demonstrated a dose–response relationship between the deteriorated neurological score in children and the maximum mercury concentration during gestation in a single strand of maternal head hair.

GUIDELINE VALUE

Almost all mercury in uncontaminated drinking-water is thought to be in the form of Hg^{2+}. Thus, it is unlikely that there is any direct risk of the intake of organic mercury compounds, and especially of alkymercurials, as a result of the ingestion of drinking-water. However, there is a real possibility that methylmercury will be converted into inorganic mercury.

In 1972, JECFA established a provisional tolerable weekly intake (PTWI) of 5 µg/kg of body weight of total mercury, of which no more than 3.3 µg/kg of body weight should be present as methylmercury (*60*). This PTWI was reaffirmed in 1978 (*61*). In 1988, JECFA reassessed methylmercury, as new data had become available; it confirmed the previously recommended PTWI for the general population, but noted that pregnant women and nursing mothers were likely to be at greater risk from the adverse effects of methylmercury. The available data were considered insufficient, however, to allow a specific methylmercury intake to be recommended for this population group (*62,63*).

To be on the conservative side, the PTWI for methylmercury was used to derive a guideline value for inorganic mercury in drinking-water. As the main exposure is from food, 10% of the PTWI was allocated to drinking-water. The guideline value for total mercury is 0.001 mg/litre (rounded figure).

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