

Arsenic in Drinking-water

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

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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.

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The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

Mr J.K. Fawell, United Kingdom (*Organic and inorganic constituents*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Dr P. Toft, Canada (*Pesticides*)
Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Treatment achievability*)

The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
Mr P. Callan, Water Sanitation and Health Programme, WHO Headquarters
Mr H. Hashizume, Water Sanitation and Health Programme, WHO Headquarters

Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

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

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
DMA	dimethylarsinic acid
DNA	deoxyribonucleic acid
IARC	International Agency for Research on Cancer
ICP-MS	inductively coupled plasma mass spectrometry
MMA	monomethylarsonic acid

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1. GENERAL DESCRIPTION

1.1 Identity

Arsenic exists in oxidation states of -3, 0, 3 and 5. It is widely distributed throughout the Earth's crust, most often as arsenic sulfide or as metal arsenates and arsenides. In water, it is most likely to be present as arsenate, with an oxidation state of 5, if the water is oxygenated. However, under reducing conditions (<200 mV), it is more likely to be present as arsenite, with an oxidation state of 3 (IPCS, 2001).

<i>Compound</i>	<i>CAS No.</i>	<i>Molecular formula</i>
Arsenic	7440-38-2	As
Arsenic trioxide	1327-53-3	As ₂ O ₃
Arsenic pentoxide	1303-28-2	As ₂ O ₅
Arsenic sulfide	1303-33-9	As ₂ S ₃
Dimethylarsinic acid (DMA)	75-60-5	(CH ₃) ₂ AsO(OH)
Monomethylarsonic acid (MMA)	124-58-3	(CH ₃)AsO(OH) ₂
Lead arsenate	10102-48-4	PbHAsO ₄
Potassium arsenate	7784-41-0	KH ₂ AsO ₄
Potassium arsenite	10124-50-2	KAsO ₂ HAsO ₂

1.2 Physicochemical properties (IARC, 1980; Lide, 1992–1993)

<i>Compound</i>	<i>Melting point (°C)</i>	<i>Boiling point (°C)</i>	<i>Density (g/cm³)</i>	<i>Water solubility (g/litre)</i>
As	613	–	5.727 at 14 °C	insoluble
As ₂ O ₃	312.3	465	3.738	37 at 20 °C
As ₂ O ₅	315 (decomposes)	–	4.32	1500 at 16 °C
As ₂ S ₃	300	707	3.43	5 × 10 ⁻⁴ at 18 °C
(CH ₃) ₂ AsO(OH)	200	–	–	829 at 22 °C
CH ₃ AsO(OH) ₂	–	–	–	–
PbHAsO ₄	720 (decomposes)	–	5.79	very slightly soluble
KH ₂ AsO ₄	288	–	2.867	190 at 6 °C
KAsO ₂ HAsO ₂	–	–	–	soluble

1.3 Major uses

Arsenicals are used commercially and industrially as alloying agents in the manufacture of transistors, lasers and semiconductors, as well as in the processing of glass, pigments, textiles, paper, metal adhesives, wood preservatives and ammunition. They are also used in the hide tanning process and, to a limited extent, as pesticides, feed additives and pharmaceuticals.

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1.4 Environmental fate

Arsenic is introduced into water through the dissolution of rocks, minerals and ores, from industrial effluents, including mining wastes, and via atmospheric deposition (IPCS, 1981; Nadakavukaren et al., 1984; Hindmarsh & McCurdy, 1986). In well oxygenated surface waters, arsenic(V) is generally the most common arsenic species present (Irgolic, 1982; Cui & Liu, 1988); under reducing conditions, such as those often found in deep lake sediments or groundwater, the predominant form is arsenic(III) (Lemmo et al., 1983; Welch et al., 1988). An increase in pH may increase the concentration of dissolved arsenic in water (Slooff et al., 1990).

2. ANALYTICAL METHODS

A silver diethyldithiocarbamate spectrophotometric method is available for the determination of arsenic; the detection limit is about 1 µg/litre (ISO, 1982). Graphite furnace atomic absorption spectroscopy, hydride generation atomic absorption spectrophotometry and inductively coupled plasma mass spectrometry (ICP-MS) are more sensitive. High-pressure liquid chromatography in combination with ICP-MS can also be used to determine various arsenic species (Irgolic, 1982).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Arsenic concentrations measured in remote or rural areas range from 0.02 to 4 ng/m³ (US NRC, 1999). In urban areas, arsenic concentrations of 3–200 ng/m³ have been measured. Much higher concentrations (>1000 ng/m³) are present in the vicinity of industrial sources (Ball et al., 1983; WHO, 1987; US NRC, 1999).

3.2 Water

The level of arsenic in natural waters, including open ocean seawater, generally ranges between 1 and 2 µg/litre (Hindmarsh & McCurdy, 1986; US NRC, 1999). Concentrations may be elevated, however, in areas with volcanic rock and sulfide mineral deposits (Hindmarsh & McCurdy, 1986); in areas containing natural sources, where levels as high as 12 mg/litre have been reported (Grinspan & Biagini, 1985); near anthropogenic sources, such as mining and agrochemical manufacture (US NRC, 1999); and in geothermal waters (mean 500 µg/litre, maximum 25 mg/litre) (US NRC, 1999). Mean arsenic concentrations in sediment range from 5 to 3000 mg/kg; the higher levels occur in areas of contamination (US NRC, 1999) but are generally unrelated to arsenic concentrations in water.

3.3 Food

The total estimated daily dietary intake of arsenic may vary widely, mainly because of wide variations in the consumption of fish and shellfish. Most data reported are for total arsenic intake and do not reflect the possible variation in intake of the more toxic

inorganic arsenic species. Limited data indicate that approximately 25% of the arsenic present in food is inorganic, but this is highly dependent upon the type of food (Hazell, 1985; US EPA, 1988; IPCS, 2001).

Fish and meat are the main sources of dietary intake of arsenic (Gartrell et al., 1986a); levels ranging from 0.4 to 118 mg/kg have been reported in marine fish sold for human consumption, and concentrations in meat and poultry can be as high as 0.44 mg/kg (Health and Welfare Canada, 1983).

The mean daily intake of arsenic in food for adults has been estimated to range from 16.7 to 129 μg (Hazell, 1985; Gartrell et al., 1986a; Dabeka et al., 1987; Zimmerli et al., 1989); the corresponding range for infants and children is 1.26–15.5 μg (Nabrzyski et al., 1985; Gartrell et al., 1986b). In preliminary studies in North America, the estimated daily intake of arsenic from the diet was 12–14 μg of inorganic arsenic (Yost et al., 1998).

3.4 Estimated total exposure and relative contribution of drinking-water

Except for individuals who are occupationally exposed to arsenic, the most important route of exposure is through the oral intake of food and drinking-water, including beverages made from drinking-water. The mean daily intake of arsenic from drinking-water will generally be less than 10 μg ; however, in those areas in which drinking-water contains elevated concentrations of arsenic, this source will make an increasingly significant contribution to the total intake of inorganic arsenic as the concentration of arsenic in drinking-water increases. Since the estimated daily intake of arsenic from food in preliminary studies of diets in North America is 12–14 μg of inorganic arsenic (Yost et al., 1998), consumption of 2 litres of drinking-water containing 10 $\mu\text{g}/\text{litre}$ would make drinking-water 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. The estimated intake from air is generally less than 1 μg .

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Ingested elemental arsenic is poorly absorbed and largely eliminated unchanged. Soluble arsenic compounds are rapidly absorbed from the gastrointestinal tract (Hindmarsh & McCurdy, 1986); arsenic(V) and organic arsenic are rapidly and almost completely eliminated via the kidneys (Buchet et al., 1981a; Luten et al., 1982; Tam et al., 1982). Inorganic arsenic may accumulate in skin, bone, liver, kidney and muscle (Ishinishi et al., 1986); its half-life in humans is between 2 and 40 days (Pomroy et al., 1980). Inorganic arsenic is eliminated from the body by the rapid urinary excretion of unchanged arsenic in both the trivalent and pentavalent forms and by sequential methylation to MMA and DMA in both 3 and 5 valence states (Buchet & Lauwerys, 1985; Lovell & Farmer, 1985). Limited short-term studies on humans indicate that the capacity to methylate inorganic arsenic is progressively, but not completely, saturated when daily intake exceeds 0.5 mg (Buchet et al., 1981b).

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The internal dose of inorganic arsenic in individuals can be determined by measuring the arsenic species in urine. The concentrations of metabolites of inorganic arsenic in urine from individuals with no known exposure to arsenic are reported to be generally below 10 µg/litre in European countries; however, in West Bengal and Bangladesh, urinary arsenic concentrations above 1 mg/litre have frequently been observed (IPCS, 2001).

In humans, inorganic arsenic does not appear to cross the blood–brain barrier; however, transplacental transfer of arsenic in humans has been reported (Gibson & Gage, 1982).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Long-term exposure

There were significant reductions in cardiac output and stroke volume in male Wistar rats and female New Zealand rabbits ingesting drinking-water containing 50 mg of arsenic(III) per litre for 18 and 10 months, respectively. In contrast, there was no effect on cardiac function in rats following ingestion of the same concentration of arsenic(V) for 18 months (Carmignani et al., 1985).

5.2 Reproductive and developmental toxicity

Teratogenic effects of arsenic in chicks, golden hamsters and mice have been reported (Hood & Bishop, 1972; Zierler et al., 1988). Arsenate was teratogenic in the offspring of pregnant hamsters following exposure on days 4–7 of gestation by minipump implantation (Ferm & Hanlon, 1985). The specific form of arsenic responsible for teratogenesis is not known, but it may be arsenite (Hanlon & Ferm, 1986). Other workers did not observe teratogenicity in studies in which mice or rabbits were orally administered arsenic acid at 0–48 mg/kg of body weight per day on gestation days 6–15 and at 0–3 mg/kg of body weight per day on gestation days 6–18, respectively (Nemec et al., 1998). The above data indicate that although arsenic is teratogenic when given by parenteral routes, it is considerably less potent when given by the oral route.

5.3 Mutagenicity and related end-points

Arsenic does not appear to induce point mutations in bacterial and mammalian assays, although it can induce chromosome breakage, chromosomal aberrations and sister chromatid exchange in a linear, dose-dependent fashion in a variety of cultured cell types, including human cells (Jacobson-Kram & Montalbano, 1985; US EPA, 1988). Arsenic(III) is about an order of magnitude more potent than arsenic(V) in this respect (US EPA, 1988). Methylated trivalent arsenic metabolites have also been reported to be genotoxic *in vitro* and to show significantly greater potency than arsenic(III) (Mass et al., 2001). Arsenic has been shown to be capable of causing chromosome damage in bone marrow cells of mice in *in vivo* assays (Deknudt et al.,

1986; Tinwell et al., 1991; Das et al., 1993; Choudhury et al., 1996). The mechanism of arsenic genotoxicity is not clear, although several mechanisms have been proposed, including reactive oxygen species and the inhibition of DNA repair (IPCS, 2001).

5.4 Carcinogenicity

Arsenic has not been found to be carcinogenic in traditional animal bioassays. In a study of the potential of arsenic compounds to act as promoters, a significant increase in the incidence of kidney tumours was observed in male Wistar rats injected intraperitoneally with a single dose of diethylnitrosamine (30 mg/kg of body weight) and, from day 7, given the maximum tolerated dose (160 mg/litre) of arsenic(III) in drinking-water for 25 weeks (Shirachi et al., 1986). Other studies using mice with specific genetic characteristics have shown carcinogenic effects (IPCS, 2001), and these may be of value in studying the potential mechanism by which arsenic causes cancer. Animal models of arsenic carcinogenicity have been extensively reviewed by Wang et al. (2002).

6. EFFECTS ON HUMANS

A number of studies have attempted to show that arsenic is an essential element, but a biological role has not been demonstrated so far (US NRC, 1999, 2001). Arsenic has not been demonstrated to be essential in humans (IPCS, 2001).

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 (arsenic(III)), the arsenates (arsenic(V)) and organic arsenic compounds. Lethal doses in humans range from 1.5 mg/kg of body weight (diarsenic trioxide) to 500 mg/kg of body weight (DMA) (Buchet & Lauwerys, 1982). Acute arsenic intoxication associated with the ingestion of well water containing 1.2 and 21.0 mg of arsenic per litre has been reported (Feinglass, 1973; Wagner et al., 1979). MMA(III) and DMA(III) are more toxic than arsenate *in vivo* and *in vitro*.

Early clinical symptoms of acute intoxication include abdominal pain, vomiting, diarrhoea, muscular pain and weakness, with flushing of the skin. These symptoms are often followed by numbness and tingling of the extremities, muscular cramping and the appearance of a papular erythematous rash (Murphy et al., 1981). Within a month, symptoms may include burning paraesthesias of the extremities, palmoplantar hyperkeratosis, Mee's lines on fingernails and progressive deterioration in motor and sensory responses (Fennell & Stacy, 1981; Murphy et al., 1981; Wesbey & Kunis, 1981).

Signs of chronic arsenicism, including dermal lesions such as hyper- and hypopigmentation, peripheral neuropathy, skin cancer, bladder and lung cancers and peripheral vascular disease, have been observed in populations ingesting arsenic-contaminated drinking-water (Tseng et al., 1968; Borgoño & Greiber, 1972; Hindmarsh et al., 1977; Tseng, 1977; Zaldivar, 1980; Zaldivar & Ghai, 1980;

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Valentine et al., 1982; Cebrian et al., 1983). Dermal lesions were the most commonly observed symptom, occurring after minimum exposure periods of approximately 5 years. Effects on the cardiovascular system were observed in children consuming arsenic-contaminated water (mean concentration 0.6 mg/litre) for an average of 7 years (Zaldivar, 1980; Zaldivar & Ghai, 1980).

In a large study conducted in Taiwan, a population of 40 421 was divided into three groups based on the arsenic content of their well water (high, >0.60 mg/litre; medium, 0.30–0.59 mg/litre; and low, <0.29 mg/litre) (Tseng, 1977). There was a clear dose–response relationship between exposure to arsenic and the frequency of dermal lesions, “blackfoot disease” (a peripheral vascular disorder) and skin cancer. However, several methodological weaknesses (e.g., investigators were not “blinded”) complicate the interpretation of the results. In addition, the possibility of other causes of blackfoot disease (e.g., humic acids in artesian well water) were not considered (Lu, 1990).

In Taiwan, the prevalence and mortality rates of diabetes mellitus were higher among the population of the blackfoot disease endemic area. There was also an exposure–response relationship between cumulative arsenic exposure and the prevalence of diabetes mellitus. A similar exposure–response pattern was observed in a study in Bangladesh, where prevalence of keratosis was used as a surrogate for arsenic exposure (US NRC, 1999, 2001; IPCS, 2001).

There have been numerous epidemiological studies that have examined the risk of various cancers associated with arsenic ingestion through drinking-water. Many of these studies 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, particularly skin, bladder and lung. In several parts of the world, arsenic-induced disease, including cancer, is a significant public health problem. The studies have been reviewed in detail (US NRC, 1999, 2001; ATSDR, 2000; IPCS, 2001). Because trivalent inorganic arsenic has greater reactivity and toxicity than pentavalent inorganic arsenic, it is generally believed that the trivalent form is the carcinogen. However, there remain considerable uncertainty and controversy over both the mechanism of carcinogenicity and the shape of the dose–response curve at low intakes. Recently, the trivalent methylated metabolites, MMA(III) and DMA(III), have been found to be more genotoxic than inorganic arsenic. The role of these metabolites with regard to arsenic carcinogenicity remains unknown.

IPCS (2001) concluded that:

Long-term exposure to arsenic in drinking-water is causally related to increased risks of cancer in the skin, lungs, bladder and kidney, as well as other skin changes such as hyperkeratosis and pigmentation changes. These effects have been demonstrated in many studies using different study designs. Exposure–response relationships and high risks have been observed for each of these end-points. The effects have been most thoroughly studied in Taiwan 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 ≤ 50 μg arsenic/litre.

7. PROVISIONAL GUIDELINE VALUE

Inorganic arsenic compounds are classified by IARC (1987) in Group 1 (carcinogenic to humans) on the basis of sufficient evidence for carcinogenicity in humans and limited evidence for carcinogenicity in animals.

Although there is a substantial database on the association between both internal and skin cancers and the consumption of arsenic in drinking-water, there remains considerable uncertainty over the actual risks at low concentrations. US NRC (2001), in its updated evaluation, concluded “that the available mode-of-action data on arsenic do not provide a biological basis for using either a linear or nonlinear extrapolation.” The maximum likelihood estimates, using a linear extrapolation, for bladder and lung cancer for US populations exposed to 10 μg of arsenic per litre in drinking-water are, respectively, 12 and 18 per 10 000 population for females and 23 and 14 per 10 000 population for males. The actual numbers, indicated by these estimated risks, would be very difficult to detect by current epidemiological methods. There is also uncertainty over the contribution of arsenic in food — a higher intake of inorganic arsenic from food would lead to a lower risk estimate for water — and the impact of factors such as variation in the metabolism of arsenic and nutritional status. 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 $\mu\text{g}/\text{litre}$, and removal of arsenic to concentrations below 10 $\mu\text{g}/\text{litre}$ is difficult in many circumstances. In view of the significant uncertainties surrounding the risk assessment for arsenic carcinogenicity and the practical difficulties in removing arsenic from drinking-water, the guideline value of 10 $\mu\text{g}/\text{litre}$ is retained. In view of the scientific uncertainties, the guideline value is designated as provisional. In many countries, this guideline value may not be attainable; where this is the case, every effort should be made to keep concentrations as low as possible.

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