Danish Ministry of the Environment
Environmental Protection Agency

Arsenic, inorganic and soluble salts

Evaluation of health hazards and proposal of a health-based quality criterion for drinking water

Environmental Project No. 1532, 2014

Title:

Arsenic, inorganic and soluble salts

Editing:

Elsa Nielsen, John Christian Larsen
Division of Toxicology and Risk Assessment
National Food Institute, Technical University of Denmark

Published by:

The Danish Environmental Protection Agency
Strandgade 29
1401 Copenhagen K
Denmark
www.mst.dk/english

Year:

Authored 2011.
Published 2014.

ISBN no.

978-87-93026-86-5

Content

Preface

This report has been prepared by Elsa Nielsen and John Christian Larsen, Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

The report has been elaborated according to the general practice laid down in the Danish EPA guidance document for the setting of health-based quality criteria for chemical substances in relation to soil, ambient air and drinking water.

The report has been subjected to review and discussion and has been endorsed by a steering committee consisting of the following representatives from Danish authorities:

- The Danish Nature Agency: Anne Christine Duer
- The Danish Ministry of Food, Agriculture and Fisheries (The Faculty of Agricultural Sciences): Niels Henrik Spliid
- The Danish Veterinary and Food Administration: Gudrun Hilbert
- The National Board of Health, Denmark, medical officer of health: Lene Garsdal
- Danish Regions: Arne Rokkjær,
- The Danish Environmental Protection Agency: Katrine Smith, Poul Bo Larsen, Finn Pedersen, Jette Rud Heltved.

1 General description

Arsenic is a naturally occurring metalloid widely distributed in the earth's crust. It can exist in four oxidation states: -3, 0, +3 and +5. Elemental arsenic is not soluble in water. In water, arsenic is mostly found in inorganic forms as oxyanions of trivalent arsenite (AsIII) or pentavalent arsenate (AsV). Under oxidising conditions, arsenate is dominant whereas, under reducing conditions, it is more likely to be present as arsenite. (WHO 2001, IARC 2004).

The aim of this evaluation is to provide the most relevant information for the setting of a health-based quality criterion for inorganic arsenicals in drinking water. Therefore, mostly information of relevance for this purpose has been considered and included in this evaluation. IARC (2004) has concluded that arsenic in drinking water is carcinogenic to humans (Group 1) and therefore, this endpoint is the main focus of this evaluation.

This document is based on the most recent evaluations prepared by WHO/IPCS (WHO 2001), WHO (2003), IARC (2004), and ATSDR (2007).

The term "arsenic" is used in a generic sense and refers to arsenic in general except when specific arsenic compounds are mentioned. The term "arsenicals" refers to arsenic compounds in general. For the purpose of comparison, concentrations and dose levels of the various arsenic compounds are expressed in terms of arsenic equivalents (As) whenever possible.

1.1 Identity and physico-chemical properties

The identity and physico-chemical properties of arsenic and selected arsenic species identified in water are presented in Table 1.

Table 1. Identity and physico-chemical properties of selected arsenic species identified in water (WHO 2001, WHO 2003, IARC 2004, ATSDR 2007)

Species	CAS-no.	Molecular formula	Molecular weight	Physical State	Melting point (°C)	Boiling point (°C)	Density (g/cm^3)	Water solubility
Arsenic	7440-38-2	As	74.92	Silver-gray or tin-white solid	817	614 (sublimes)	5.73	Insoluble
Inorganic arsenic, trivalent								
Arsenic trioxide	1327-53-3	As_2O_3	197.84	White solid	313	460	3.8	37 g/l at 20°C
Sodium arsenite	7784-46-5	$NaAsO_2$	130.92	White to gray-white solid	-	-	1.87	Freely soluble
Inorganic arsenic, pentavalent								
Arsenic acid (arsenate)	7778-39-4	$AsO(OH)_3$	141.94	White solid	35	Loses H_2O at 160	~2.2	302 g/l at 12.5°C
Arsenic pentoxide	1303-28-2	As_2O_5	229.84	White solid	~300 (decom-poses)	-	4.32	2300 g/l at 20°C
Sodium arsenate	7778-43-0	Na_2HAsO_4	185.91	Colour-less solid	57	-	1.87	1:3 parts

1.2 Production and use

Arsenic is obtained as a by-product of the smelting of copper, lead, cobalt, and gold ores. Arsenic trioxide is volatilised during smelting and accumulates in the flue dust. Elemental arsenic can be prepared by the reduction of arsenic trioxide with charcoal. (ATSDR 2007, WHO 2001).

It has been estimated that about 70% of the world arsenic production is used in wood preservatives especially in timber treatment as copper chrome arsenate (CCA), 22% in agricultural chemicals, and the remainder in glass (4%), non-ferrous alloys (2%) and other uses (2%) including pharmaceuticals and semiconductors. (WHO 2001).

In Denmark, arsenic is used in construction materials (2007: 1.4 tonnes) (MST 2009).

1.3 Environmental occurrence and fate

Arsenic and its compounds are ubiquitous in nature and occur in both organic and inorganic forms. Arsenic is present in more than 200 mineral species, the most common of which is arsenopyrite. Concentrations of various types of igneous rocks range from < 1 to 15 mg As/kg, with a mean value of 2 mg As/kg. Similar concentrations (< 1-20 mg As/kg) are found in sandstone and limestone. (WHO 2001).

Mining, smelting of non-ferrous metals and burning of fossil fuels are the major industrial processes that contribute to anthropogenic arsenic contamination of air, water and soil. Historically, use of arsenic-containing pesticides has led to contamination of agricultural land. The use of arsenic in the preservation of timber has also led to contamination of the environment. (WHO 2001, ATSDR 2007).

Three major modes of arsenic biotransformation have been found to occur in the environment: redox transformation between arsenite and arsenate, the reduction and methylation of arsenic, and the biosynthesis of organoarsenic compounds. There is biogeochemical cycling of compounds formed from these processes. (WHO 2001).

1.3.1 Air

Arsenic is emitted into the atmosphere by high-temperature processes such as coal-fired power generation plants, burning vegetation and volcanism. It has been estimated that about one-third of the atmospheric flux of arsenic is of natural origin. Volcanic action is the most important natural source of arsenic. (WHO 2001).

Arsenic is released into the atmosphere primarily as arsenic trioxide and exists mainly adsorbed on particulate matter. These particles are dispersed by the wind and are returned to the earth by wet or dry deposition. (ATSDR 2007, WHO 2001).

Typical background levels for arsenic in the atmosphere are 0.2-1.5 ng/m^3 for rural areas, 0.5-3 ng/m^3 for urban areas, and < 50 ng/m^3 for industrial sites (DG Environment 2000 – quoted from WHO 2001).

1.3.2 Water

Arsenic is introduced into water through the dissolution of rocks, minerals and ores, from industrial effluents including mining wastes, and via atmospheric deposition. In water, inorganic arsenic occurs primarily in two oxidation states, pentavalent (arsenate) and trivalent (arsenite). Both forms generally co-exist, although arsenate predominates under oxidising conditions and arsenite predominates under reducing conditions. Arsenic may undergo a variety of reactions in the environment, including oxidation-reduction reactions, ligand exchange, precipitation, and biotransformation. These reactions are influenced by the oxidation-reduction potential, pH, metal sulphide and sulphide ion concentrations, iron concentration, temperature, salinity, and distribution and composition of the biota. Much of the arsenic will adsorb to particulate matter and sediment. (ATSDR 2007, WHO 2001, WHO 2003, IARC 2004).

Concentrations of arsenic in open ocean seawater are typically 1-2 µg/litre and concentrations in rivers and lakes are generally below 10 µg/litre, although higher levels may occur near natural mineral deposits or anthropogenic sources. Arsenic levels in groundwater average about 1-2 µg/litre except in areas with volcanic rock and sulphide mineral deposits where arsenic levels can be up to 3 mg/litre. Mean sediment arsenic concentrations range from 5 to 3000 mg/kg, with the higher levels occurring in areas of contamination. (WHO 2001, WHO 2003, IARC 2004, ATSDR 2007).

In Denmark (2006), the concentration of arsenic ranged from 0-3.75 µg/litre in 557/686 groundwater samples, from 3.75-5 µg/litre in 29/686 samples, and >5

µg/litre in 100/686 samples. In the period 1993-2006 (5140 groundwater samples), a mean concentration of 3.20 µg/litre was reported with a maximum value of 120 µg/l. (GEUS 2007).

In Denmark (896 samples of groundwater during 1990-97), a mean concentration (median) of 0.76 µg As/l was found with the 90% percentile being 5.7 µg As/l (GEUS 1998).

In Denmark, the concentration of arsenic has been measured in 4833 groundwater (raw water) samples in the period from 1991-2006. In 83% of the samples, the concentration of arsenic was below the limit value of 5 µg/litre. In 10% of the samples, the concentration was between 5 and 10 µg/litre, and in the remaining 7% of the samples, the concentration was above 10 µg/litre. The median values from 2% of the samples showed a concentration of arsenic above 20 µg/litre. (BLST 2009).

1.3.3 Soil

Arsenic found in soil either naturally occurring or from anthropogenic releases forms insoluble complexes with iron, aluminium, and magnesium oxides found in soil surfaces, and in this form, arsenic is relatively immobile. However, under reducing conditions, arsenic can be released from the solid phase, resulting in soluble mobile forms of arsenic, which may potentially leach into groundwater or result in runoff of arsenic into surface waters. (ATSDR 2007).

The ability of arsenic to bind to sulphur ligands means that it tends to be found associated with sulphide-bearing mineral deposits, either as separate arsenic minerals or as a trace of a minor constituent of the other sulphide minerals. This leads to elevated levels in soils in many mineralised areas where the concentrations of associated arsenic can range from a few milligrams to more than 100 mg/kg. (WHO 2001, IARC 2004).

Speciation determines how arsenic compounds interact with their environment. For example, the behaviour of arsenate and arsenite in soil differs considerably. Movement in environmental matrices is a strong function of speciation and soil type. Soil pH also influences arsenic mobility. At a pH of 5.8 arsenate is slightly more mobile than arsenite, but when pH changes from acidic to neutral to basic, arsenite increasingly tends to become the more mobile species, though mobility of both arsenite and arsenate increases with increasing pH In strongly adsorbing soils, transport rate and speciation are influenced by organic carbon content and microbial population. Both arsenite and arsenate are transported at a slower rate in strongly adsorbing soils than in sandy soils. Under oxidising and aerated conditions, the predominant form of arsenic in soil is arsenate. Under reducing and waterlogged conditions, arsenites should be the predominant arsenic compounds. The rate of conversion is dependent on the redox potential and pH of the soil as well as on other physical, chemical and biological factors. In brief, at moderate or high redox potential, arsenic can be stabilised as a series of pentavalent (arsenate) oxyanions. However, under most reducing (acid and mildly alkaline) conditions, arsenite predominates. (WHO 2001).

Arsenic is found in the earth's crust at an average level of 2 mg/kg. Background concentrations in soil range from 1 to 40 mg/kg, with a mean of 5 mg/kg, although much higher levels may occur in mining areas, at waste sites, near high geological deposits of arsenic-rich minerals, or from pesticide application. (ATSDR 2007, WHO 2001).

The concentration of arsenic in Danish soils was 3.3 mg As/kg (median, dry weight) with the 95% percentile being 8.4 mg As/kg (DMU 1996).

Two projects have investigated the diffuse soil pollution in urban areas.
In one project, the concentration of arsenic in soil around a former rolling mill station on Amager was measured. The level of arsenic in the soil was about 4-10 mg/kg dry weight. (MST 2004a).
In the other project, different areas in Copenhagen and Ringsted were investigated. The level of arsenic in the soil was 2.7 mg/kg - 6.4 mg/kg (dry weight). There were no differences in arsenic levels in soil according to the age of the urban areas. No differences in arsenic levels between soil in Ringsted and Copenhagen were observed, and the concentrations did not decline with depth. (MST 2004b).
The two reports concluded that the levels found in urban areas correspond to the background level in country areas.

1.3.4 Bioaccumulation

Marine organisms normally contain arsenic residues ranging from 1-2 mg/kg to more than 100 mg/kg, predominantly as organic arsenic species such as arsenosugars (macroalgae) and arsenobetaine (invertebrates and fish). Bioaccumulation of organic arsenic compounds, after their biogenesis from inorganic forms, occurs in aquatic organisms. Bioconcentration factors (BCFs) in freshwater invertebrates and fish for arsenic compounds are lower than for marine organisms. Biomagnification in aquatic food chains has not been observed. Background arsenic concentrations in freshwater and terrestrial biota are usually less than 1 mg/kg (fresh weight).
Terrestrial plants may accumulate arsenic by root uptake from the soil or by adsorption of airborne arsenic deposited on the leaves. Arsenic levels are higher in biota collected near anthropogenic sources or in areas with geothermal activity. Some species accumulate substantial levels, with mean concentrations of up to 3000 mg/kg at arsenical mine sites.
(WHO 2001).

1.3.5 Foodstuffs

Arsenic is found in many foods, at concentrations that usually range from 20 to 140 µg/kg; however, total arsenic concentrations may be substantially higher in certain seafoods. Meats and cereals have generally higher concentrations than vegetables, fruit and dairy products. The actual total arsenic concentrations in foodstuffs from various countries will vary widely depending on the food type, growing conditions (type of soil, water, geochemical activity, use of arsenical pesticides) and processing techniques. (WHO 2001, ATSDR 2007).

Although most monitoring data is given as the concentration of total arsenic, arsenic in foods is a mixture of inorganic and organic arsenicals. The general consensus in the literature is that about 85->90% of the arsenic in the edible parts of marine fish and shellfish is organic arsenicals (e.g., arsenobetaine, arsenocholine, dimethylarsinic acid) and that approximately 10% is inorganic arsenic. On the basis of limited data, it has been estimated that the percentage of inorganic arsenic is about 75% in meats, 65% in poultry, 75% in dairy products, and 65% in cereals. In fruits and vegetables, the organic species predominate with inorganic arsenic contributing 10% and 5%, respectively. On the basis of these

preliminary data it has been estimated that approximately 25% of the daily intake of dietary arsenic is inorganic. (WHO 2001, ATSDR 2007).

In Denmark (1998-2003), arsenic was mainly found in marine foods with average concentrations in fish ranging from 352 to 10700 µg As/kg fresh weight. The contents found in fish greatly varied for the same fish species. Part of the variation in the arsenic content found in flounder, herring and cod could be explained by salinity differences between the seas where the fish was caught. In general, the arsenic contents were high in fish caught in waters with a high salinity (The North Sea and The Kattegat) and low in more brackish waters (The Belt Sea and The Baltic). Average concentrations (µg As/kg fresh weight) in other foods were <5-56 (meat including liver and kidney as well as poultry), 1-7 (dairy products), 0.5-8 (vegetables), about 20 (mushrooms), and 2-9 (beverages). (FDIR 2005)

1.4 Human exposure

Non-occupational human exposure to arsenic in the environment is primarily through the ingestion of food and water, but contaminated ambient air and soil are also potential sources of exposure to arsenic.

For most people, diet is the largest source of exposure to arsenic. Fish, meat and poultry are the main sources of dietary intake of arsenic. The total estimated daily 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 compounds. Limited data indicate that approximately 25% of the arsenic present in food is inorganic, but this depends highly on the type of food ingested. Inorganic arsenic levels in fish and shellfish are low (< 1-10%) whereas foodstuffs such as meat, poultry, dairy products and cereals have higher levels of inorganic arsenic. (WHO 2001, WHO 2003).

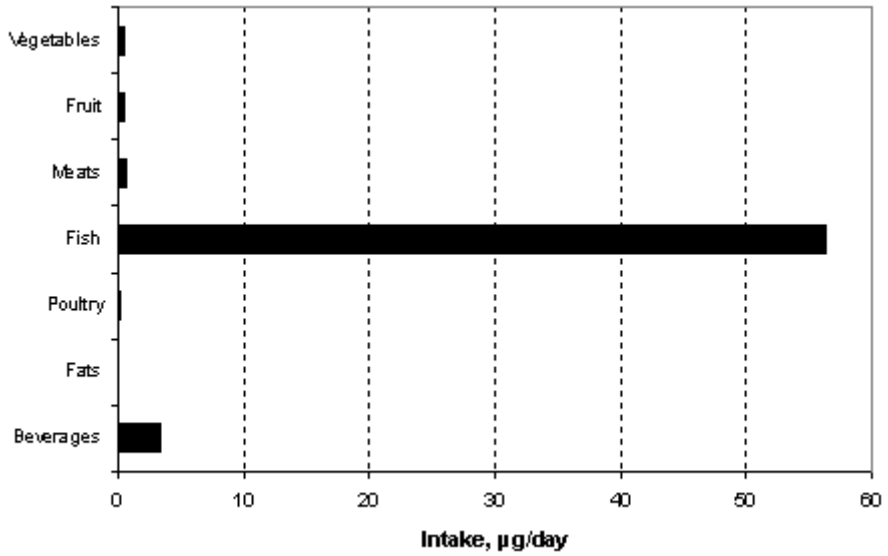
The daily intake of total arsenic from food and beverages is generally between 20 and 300 µg/day (WHO 2001).

In Denmark, the mean intake of arsenic from the total diet (1998-2003, based on arsenic in vegetables, meat, poultry, fish and beverages) was estimated at 62 µg/day (0.9 µg/bw/day) for adults (15-75 years) with a 95th percentile of 227 µg/day (3.2 µg/bw/day). A vast majority of the intake (91% of the total intake) was from fish, as shown in Figure 1. Assuming that inorganic arsenic occurs in fish and other seafood products at 5% of the total arsenic, the intake of the inorganic forms via seafood corresponds to 2% of the PTWI value for inorganic arsenic (15 µg/bw/week or 154 µg/person/day). (FDIR 2005).

The European Food Safety Authority has recently published a scientific opinion on arsenic in Food (EFSA 2009). More than 100,000 occurrence data on arsenic in food were considered with approximately 98% reported as total arsenic. Making a number of assumptions for the contribution of inorganic arsenic to total arsenic, the inorganic arsenic exposure from food and water across 19 European countries, using lower bound and upper bound concentrations, has been estimated to range from 0.13 to 0.56 µg/kg bw/day for average consumers, and from 0.37 to 1.22 µg/kg bw/day for 95 percentile consumers. High consumers of rice in Europe are estimated to have a daily dietary exposure of inorganic arsenic of about 1 µg/kg bw/day and high consumers of algae-based products can have dietary exposure of inorganic arsenic of about 4 µg/kg bw/day. Children under three years of age are the most exposed to inorganic arsenic; two different studies show an inorganic

arsenic intake ranging from 0.50 to 2.66 µg/kg bw/day, i.e., in general about 2-3 fold that of adults.

Figure 1. Intake of arsenic from main food groups by Danes aged 15-75 years



The mean daily intake of arsenic from drinking water will generally be less than 10 µg/day. However, in those areas where drinking-water has higher concentrations of arsenic, this source will make an increasing contribution to the total daily intake of inorganic arsenic as the concentration of arsenic in drinking-water increases. (WHO 2003).

Using the mean value for the concentration of arsenic in Danish groundwater of 3.2 µg As/l (1993-2006), and the consumption rate of 0.03 l/kg bw/day (median value for children 1-10 years old), the intake from drinking-water would be 0.1 µg As/kg bw/day (assuming no dilution of groundwater). For an adult, assuming an average consumption rate of 1.4 litre/day, the daily exposure to arsenic from drinking water would be 4.5 µg/day (about 0.06 µg As/kg bw/day assuming an adult body weight of 70 kg).

Contaminated soil is also a potential source of arsenic exposure. Using the median value for the soil concentration in Denmark of 3.3 mg As/kg soil, and an intake of 0.0001 kg soil/day (median value for children 1-3 years old), the intake from soil would be 0.03 µg As/kg bw/day (body weight of 13 kg).

Inhalation of contaminated air is also a potential source of arsenic exposure. Using the upper value for the range of the typical background levels for arsenic in the atmosphere of 3 ng/m^3 for urban areas as a reasonable worst case scenario, and assuming the inhalation rate as 0.5 m^3/kg bw/day (for children 1-5 years old), the inhalation exposure to arsenic would be 1.5 ng As/kg bw/day. For an adult, assuming an average inhalation rate as 13 m^3/day, the daily inhalation exposure to arsenic from ambient air would be about 39 ng/day (about 0.6 ng As/kg bw/day assuming an adult body weight of 70 kg).

Table 2 summarises the exposure to arsenic from the various media as estimated according to the approach generally applied according to the principles for setting health-based quality criteria for chemical substances in ambient air, soil and drinking water.

Table 2. Estimated exposures from various media

Medium	Adults (body weight 70 kg)		Children (1-2/3 years)	
	Average	High exposure	Average	High exposure
Ambient air [a)]	0.6 ng As/ kg bw/day	-	1.5 ng As/kg bw/day	-
Drinking water [b)]	0.06 µg As/ kg bw/day	-	0.1 µg As/kg bw/day	-
Soil	-	-	0.03 µg As/kg bw/day [e)]	-
Diet	0.9 µg As/ kg bw/day [c)]	3.2 µg As/ kg bw/day [d)]	-	-

a) Based on a typical arsenic ambient air concentration of 3 ng As/m^3.

b) Based on a mean value for the concentration of arsenic in Danish groundwater of 3.2 µg As/l.

c) Based on the mean intake of arsenic from the total diet.

d) Based on the 95th percentile for intake of arsenic from the total diet.

e) Based on a median value for the concentration of arsenic in Danish soil of 3.3 mg As/kg soil.

2 Toxicokinetics

Humans are exposed to many different forms of inorganic and organic arsenic species (arsenicals) in food, water and other media. Study of the kinetics and metabolism of arsenicals in animals and humans can thus be quite complex, as a result of differences in physico-chemical properties and bioavailability of the various forms of arsenic. Arsenic metabolism is also characterised by relatively large qualitative and quantitative interspecies differences.

The information in this section is summarised based on the data reported in the most recent evaluations prepared by WHO/IPCS (WHO 2001), WHO (2003), IARC (2004), ATSDR (2007), and EFSA (2009). Therefore, references are generally not stated except in the cases where information from a specific study or evaluation has been included.

2.1 Absorption

2.1.1 Oral intake

The bioavailability of ingested inorganic arsenic will vary depending on the matrix in which it is ingested (e.g. food, water, beverages, soil), the solubility of the arsenical compound itself, and the presence of other food constituents and nutrients in the gastrointestinal tract.

Controlled ingestion studies in humans indicate that both trivalent and pentavalent arsenic compounds are rapidly and well absorbed from the gastrointestinal tract with between 45 and 75% of the dose of various inorganic forms of arsenic being excreted in the urine within a few days.

Soluble arsenates and arsenites are rapidly and extensively absorbed from the gastrointestinal tract of common laboratory animals (rat, mouse, rabbit, hamster) after administration of a single oral dose.
Data from mouse studies (Vahter & Norin 1980 – quoted from WHO 2001) indicate that arsenite may be more extensively absorbed from the gastrointestinal tract than arsenate at lower doses (0.4 mg As/kg; arsenite 90%, arsenate 77%), whereas the reverse appears to occur at higher doses (4.0 mg As/kg; arsenite 65%, arsenate 89%). About the same percentage faecal elimination was observed following the same dose given orally and subcutaneously, indicating a nearly complete gastrointestinal absorption. It should be noted that the mice in this study were not fed for at least 2 hours before and 48 hours after dosing.
Another mouse study (Odanaka et al. 1980 – quoted from WHO 2001) indicated that much less pentavalent arsenic is absorbed from the gastrointestinal tract after oral administration with 48.5% of the dose (5 mg/kg) being excreted in the urine. It should be noted that the mice in this study were not food restricted.

The bioavailability of arsenic from soils has been assessed using various animal models. These studies indicate that oral bioavailability of arsenic in a soil or dust vehicle is often lower than that of the pure soluble salts typically used in toxicity studies. However, bioavailability is substantially dependent on the soil type.

One study (Ng et al. 1998 – quoted from WHO 2001), using a rat model, has reported the absolute bioavailability of arsenic in soils containing 32-1597 µg As/kg from a combination of arsenical pesticides and natural geological formations in a residential area to be about 1-10% relative to arsenite and 0.3-3% relative to arsenate.

2.1.2 Dermal contact

One study (Wester et al. 1993 – quoted from WHO 2001 and IARC 2004) is available regarding the percutaneous absorption of arsenic (arsenic acid) from water and soil both *in vivo* using rhesus monkeys and *in vitro* with human skin. *In vivo*, absorption of arsenic acid from water was about 6% at the low dose (0.024 ng/cm^2) and about 2% at the high dose (2.1 µg/cm^2). Absorption from soil was about 5% at the low dose (0.04 ng/cm^2) and about 3% at the high dose (0.6 µg/cm^2). For human skin *in vitro*, 1.9% was absorbed from water and 0.8% from soil at the low dose over a 24-hour period.

2.2 Distribution

Inorganic arsenic is rapidly cleared from blood in humans and in most common laboratory animals, including mice, rabbits, and hamsters. In rats, however, the presence of arsenic in the blood is prolonged due to accumulation in erythrocytes. It appears that rat haemoglobin specifically binds dimethylarsinic acid (DMA), and this greatly increases the biological half-life of inorganic arsenic and DMA in rats. Although clearance of both arsenate and arsenite from blood in other mammalian species is rapid, differences dependent on both valence state and dose have been observed.

Post-mortem analysis of human tissues has revealed that arsenic is widely distributed in the body after either long-term relatively low-level exposure or poisoning. Arsenic concentrations are quite low in brain relative to other tissues and inorganic arsenic is the predominant form in tissues, followed by DMA. Inter-individual variation in total tissue arsenic is generally quite high. Data suggest that arsenic accumulates in tissues with age.
Case reports of arsenic poisoning in pregnant women resulting in death of the foetus accompanied by toxic levels of arsenic in foetal organs and tissues demonstrate that arsenite readily passes through the placenta. A recent study (Concha et al. 1998 – quoted from WHO 2001 and IARC 2004) reported that arsenic concentrations were similar in cord blood and maternal blood (~9 µg/litre) of maternal-infant pairs exposed to drinking-water containing high levels of arsenic (~200 µg/litre). Placentas also had elevated concentrations of arsenic. More than 90% of the arsenic in urine and plasma of both newborns and their mothers (at the time of delivery) was in the form of DMA, compared with about 70% in non-pregnant women, indicating an increase in arsenic methylation during pregnancy.

Studies in rats, mice, rabbits, hamsters and monkeys demonstrate that arsenic, administered orally, in either the trivalent or pentavalent form, is rapidly distributed throughout the body and arsenic is generally present in all tissues.

Comparative studies of arsenate and arsenite distribution at comparable dose levels indicate that, in general, concentrations of arsenic in organs tended to be higher after administration of arsenite than of arsenate, with the exception of the skeleton. This latter finding was ascribed to arsenate being a structural analogue of phosphate and substituting for it in the apatite crystal of bone. The greater retention

of arsenite in tissues is a consequence of its reactivity and binding with tissue constituents, most notably sulfhydryl groups.

Both species-specific and valence-state-dependent differences have been demonstrated in the biliary excretion of arsenic. Excretion of trivalent arsenic into the bile is much more extensive in rats than in rabbits or dogs. Arsenite is excreted to a greater extent than arsenate in the bile of rats and mice. Mechanistic studies indicate that transport of either arsenate or arsenite into the bile of rats is dependent on GSH and it has been demonstrated in recent studies that arsenite as well as other trivalent arsenicals directly form complexes with glutathione (GSH).

Numerous studies have revealed that skin, hair, and tissues high in squamous epithelium (e.g. mucosa of the oral cavity, oesophagus, stomach and small intestine) have a strong tendency to accumulate and maintain higher levels of arsenic. This is apparently a function of the binding of arsenic to keratin in these tissues.

Arsenic can cross the blood-brain barrier and it has been found in brain tissue after oral administration of trivalent or pentavalent inorganic arsenic. However, the levels are generally low both across time and relative to other tissues, which indicates that arsenic does not readily cross the blood-brain barrier or accumulate in brain tissue after acute dosing.

Studies have documented the ability of trivalent and pentavalent inorganic arsenic to cross the placenta in laboratory animals. The rate of placental transfer was lower in marmoset monkeys (non-methylating species) than in mice, possibly a consequence of stronger binding in maternal tissues. Studies indicate that much of the arsenic reaching the foetus after oral administration has already been transformed to the less acutely toxic methylated metabolites.

The sub-cellular distribution of total arsenic administered as either sodium arsenate or sodium arsenite has been studied in mice, rats, rabbits and marmoset monkeys. In general, the sub-cellular localisation and retention of arsenic accounts for its much slower elimination in rats than in other species. In rats, arsenic is strongly associated with high-molecular-weight cellular components in liver and kidney, whereas in rabbits, it is associated with low-molecular-weight, more readily diffusible cellular components. It has also been reported that, in the marmoset monkey, arsenic (administered as arsenite or arsenate) shows a unique strong tendency to bind with the rough endoplasmic reticulum in the liver that had not been observed in other laboratory animals.

2.3 Metabolism and excretion

In many species, arsenic metabolism is characterised by two main types of reactions: (1) reduction reactions of pentavalent to trivalent arsenic, and (2) oxidative methylation reactions in which trivalent forms of arsenic are sequentially methylated to form mono-, di- and trimethylated products using S-adenosyl methionine (SAM) as the methyl donor and GSH as an essential co-factor. Methylation of inorganic arsenic facilitates the excretion of inorganic arsenic from the body, as the end-products MMA and DMA are readily excreted in urine.

Urine is the primary route of excretion for both pentavalent and trivalent inorganic arsenicals in most common laboratory animals as well in humans.
Studies in adult human males voluntarily ingesting a known amount of either trivalent or pentavalent arsenic indicate that 45-75% of the dose is excreted in the

urine within a few days to a week. The main metabolites excreted in the urine of humans exposed to inorganic arsenic are mono- and dimethylated arsenic acids, together with some unmetabolised inorganic arsenic. The relative amounts of the species in urine are generally 10-30% inorganic arsenic, 10-20% MMA, and 60-80% DMA.
With the exception of the rat, which exhibits slower overall elimination of arsenic, 50% or more of a single oral dose of arsenic administered to laboratory animals is usually eliminated in urine within 48 hours. Urine is also the primary route of elimination in species such as the marmoset which do not methylate arsenic.

The metabolism and disposition of inorganic arsenic may be influenced by its valence state, particularly at high dose levels. Studies in laboratory animals indicate that administration of trivalent inorganic arsenic initially results in higher levels in most tissues than does the administration of pentavalent arsenic. However, the trivalent form is more extensively methylated, leading to similar long-term excretion.

Due to the ability of arsenic to accumulate in keratin-containing tissues, skin, hair and nails could also be considered potential excretory routes for arsenic, although they would in general be quantitatively minor.
Levels of arsenic or its metabolites in blood, hair, nails and urine are used as biomarkers of arsenic exposure. Blood arsenic is a useful biomarker only in the case of acute arsenic poisoning or stable chronic high-level exposure. Arsenic is rapidly cleared from blood, and speciation of its chemical forms in blood is difficult. Arsenic in hair and nails can be indicators of past arsenic exposure. Arsenic in hair may also be used to estimate relative length of time since an acute exposure. Metabolites in urine, expressed either as inorganic arsenic or as the sum of metabolites (inorganic arsenic + MMA + DMA), reflect the absorbed dose of inorganic arsenic on an individual level and provide the best quantitative estimate of recently absorbed dose of arsenic. Generally, it ranges from 5 to 20 µg As/litre, but may even exceed 1000 µg/litre.

Arsenic can be excreted in human milk, although the levels are low.

2.4 Interspecies and inter-individual differences

There are pronounced interspecies differences in the elimination of arsenic. Most experimental animals excrete very little MMA in urine compared with humans. Some species, in particular guinea-pigs and several species of non-human primates (e.g. marmoset monkeys and chimpanzees) are unable to methylate inorganic arsenic at all whereas in humans and most common laboratory animals, inorganic arsenic is extensively methylated. In addition, rats show different kinetics of arsenic metabolism with a pronounced accumulation of dimethyl arsinous acid (DMAIII) in red blood cells and greater biliary excretion of arsenic compared with humans.

Although a number of studies have shown that the average relative distribution of arsenic metabolites in the urine in humans is 10-30% inorganic arsenic, 10-20% MMA, and 60-80% DMA, there is a wide variation among individuals. Differences between population groups have also been reported. Factors such as dose, age, gender and smoking contribute only minimally to the large inter-individual variation in arsenic methylation observed in humans. Studies in humans suggest the existence of a wide difference in the activity of methyltransferases, and the existence of polymorphism has been hypothesised. Data indicate that the influence

of genetic polymorphism is more important than environmental factors for the variation in arsenic methylation.

A few studies have indicated a slightly larger fraction of urinary MMA and a smaller fraction of DMA in individuals with arsenic-related health effects, including skin lesions and chromosomal aberrations. There are indications that a relatively large amount of MMA in urine is associated with greater retention of arsenic in the body. Data from a number of experimental studies on humans indicates that a higher percentage of DMA in urine is associated with greater overall excretion, while a higher percentage of inorganic arsenic and MMA is associated with slower excretion of total arsenic metabolites.
Similarly, other mammals that excrete little (rat, mouse rabbit, hamster, Beagle dog) or no MMA (guinea-pig, marmoset, chimpanzee) in the urine, that is, most experimental animals, show a rapid overall excretions of arsenic. They also seem to be less susceptible than humans to arsenic-induced toxicity, including cancer.

Compared with inorganic arsenic, the methylated metabolites containing pentavalent arsenic are less cytotoxic, less reactive with tissue constituents and more readily excreted in the urine. This has been taken as evidence that methylation of arsenic is an efficient detoxification process. In general, trivalent arsenic is considered more toxic than the pentavalent form; however, recent studies have shown that the trivalent methylated metabolites are considerably more toxic than inorganic trivalent arsenic. Thus, their presence in tissues and body fluids implies that the metabolism of inorganic arsenic involves important bioactivation processes, and that the toxicity of inorganic arsenic probably depends on its metabolism, especially the capacity of cells to produce methylated intermediates that react with tissue constituents. A more complete understanding of the mechanisms of the metabolism of arsenic will provide further insight into the factors determining susceptibility to its toxicity. (IARC 2004).

According to IARC (2004), it is difficult to evaluate human metabolism of arsenic based on much of the available experimental animal data. Hamsters and rabbits seem to be the most useful because their metabolism is most similar to that in humans. IARC did not take rat data into account in their evaluation due to the species difference in toxicokinetics and metabolism between humans and rats.

2.5 Mode of action

Trivalent inorganic arsenicals (arsenite) readily react with sulfhydryl groups such as GSH and cysteine. The activity of enzymes or receptors is due in part to the functional groups on amino acids such as the sulfhydryl group on cysteine or coenzymes such as lipoic acid, which has vicinal thiol groups. Thus, if arsenite binds to a critical thiol or dithiol, the enzyme may be inhibited. Arsenite inhibits pyruvate dehydrogenase, a lipoic-acid-dependent enzyme involved in gluconeogenesis. The acute toxicity of inorganic arsenic may result in part from inhibition of gluconeogenesis and ultimately depletion of carbohydrates from the organism.

One potential mechanism for the toxicity of pentavalent inorganic arsenic (arsenate) is the reduction to a trivalent inorganic form (arsenite), which occurs *in vivo*. Arsenite is more toxic than arsenate, as evidenced by the lower doses needed to elicit a toxic response. Another potential mechanism is the replacement of phosphate with arsenate. In the human erythrocyte, arsenate can replace phosphate in the sodium pump and the anion exchange transport system. Arsenate can form esters with glucose and gluconate, forming glucose-6-arsenate and 6-

arsenogluconate, respectively, compounds that resemble glucose-6-phosphate and 6-phosphogluconate.
Arsenate uncouples *in vitro* oxidative phosphorylation because it has a similar structure to phosphate. Two mechanisms for this effect, termed arsenolysis, have been proposed. During glycolysis, arsenate can substitute for phosphate to form an arsenic anhydride which is unstable and hydrolyses. Normally ATP is generated during glycolysis, but with arsenate present instead of phosphate, ATP is not formed. Adenosine-5'-diphosphate-arsenate is synthesised by sub-mitochondrial particles from adenosine-5'-diphosphate (ADP) and arsenate in the presence of succinate. ADP-arsenate hydrolyses more easily than ATP. The formation and hydrolysis of ADP-arsenate result in arsenolysis.

IARC (2004) has concluded that arsenic in drinking water is carcinogenic to humans. Because trivalent inorganic arsenic has a greater reactivity and toxicity than pentavalent inorganic arsenic, it is generally believed that the trivalent form is the active carcinogenic species.
Arsenic is not a point mutagen but induces chromosomal abnormalities including changes in structure and number of chromosomes, endo-reduplication and sister chromatid exchanges. DNA repair is inhibited by arsenic, and this inhibition can result in a co-mutagenic effect with several chemicals. There are some indications that arsenite does not directly inhibit DNA ligase, but affects repair processes controlled by the cell. Hypermethylation of DNA, particularly the promoter region, can result in inactivation of tumour suppressor genes or genes involved in DNA repair. It has been shown that arsenite inhibits the ubiquitin-dependent proteolytic pathway and suggested that the gene product, or a component within the ubiquitin[1] system, is targeted by arsenic, resulting in alterations that may result in genotoxicity and carcinogenicity.

[1] Ubiquitin is a small protein that is ubiquitously expressed in eukaryotes. The most prominent function of ubiquitin is labelling proteins for proteasomal degradation. Besides this function, ubiquitin also controls the stability, function, and intracellular localisation of a wide variety of proteins.

3 Human toxicity

Arsenic has long been known because of its acute and long-term toxicity. Arsenic has effects on widely different organ systems in the body.

In humans, most cases of toxicity have resulted from accidental, suicidal, homicidal, or medicinal ingestion of arsenic-containing powders or solutions or by consumption of contaminated food or drinking water. In some cases (e.g., medicine), the chemical form is known, but in many cases (e.g., exposures through drinking water), the chemical form is not known. In these cases, it is presumed that the most likely forms are either inorganic arsenate or inorganic arsenite, or a mixture.

As the aim of this evaluation is to provide the most relevant information for the setting of a health-based quality criterion for inorganic arsenicals in drinking water, only information of relevance for this purpose has been considered and included in this evaluation, i.e., the focus is on oral intake. IARC (2004) has concluded that arsenic in drinking water is carcinogenic to humans (Group 1) and therefore, this endpoint is the main focus of this evaluation. Consequently, only short summaries on other end-points have been included in this section.

The information in this section is summarised based on the data reported in the most recent evaluations prepared by WHO/IPCS (WHO 2001), WHO (2003), IARC (2004), ATSDR (2007), and EFSA (2009). Therefore, references are generally not stated except in the cases where information from a specific study or evaluation has been included.

3.1 Acute toxicity

Inorganic arsenic is acutely toxic, and ingestion of large doses leads to gastrointestinal symptoms, disturbances of cardiovascular and central nervous system functions, multiorgan failure and eventually death. In survivors, bone marrow depression, haemolysis, hepatomegaly, melanosis, polyneuropathy and encephalopathy may be observed.

A precise estimate of the ingested dose is usually not available in acute poisonings, so quantitative information on lethal and non-lethal doses in humans is sparse. Lethal oral doses of 2-21 g (28-300 mg/kg bw) arsenic have been reported. Cases with non-fatal outcome (usually after treatment and often with permanent neurological sequelae) have been reported after oral doses of 1-16 g (14-230 mg/kg bw) arsenic. Serious, non-fatal intoxications in infants have been observed after doses of 0.7 mg, 9-14 mg, and 2400 mg of arsenic trioxide.

3.2 Chronic toxicity

Manifestations of chronic arsenic toxicity (chronic arsenicalism) include dermal effects, vascular diseases, neurological effects, liver effects, gastrointestinal disturbances, and chronic lung disease. Exposure to arsenic has also been associated with an increased risk for diabetes mellitus. These effects have been

reported from different regions of the world where the content of arsenic in drinking-water is elevated.

3.2.1 Levels of arsenic in drinking−water in epidemiological studies

The following summary is based primarily on WHO (2001).

Extensive information concerning health effects of ingestion of inorganic arsenic in drinking-water comes from a series of studies performed in Taiwan. In the late 1960s, chronic arsenic exposure from drinking-water in Taiwan was suggested to be the cause of ”Blackfoot disease” (BFD), a severe form of peripheral vascular disease which leads to gangrenous changes.

An early study (1962) reported median well-water arsenic concentration in four BFD-endemic villages was 780 µg As/litre (range 350-1100). In another early report (1968), the mean well-water arsenic concentration in 11 villages in the endemic area was reported to be 520 µg/litre (range 342-896 µg/litre). Similar concentrations of arsenic (mean 590, range 240-960 µg/litre) were reported in 13 deep well-water samples (1961). In a later (1968), more extensive report, based on 126 analyses from 29 villages in the BFD-endemic area, the average arsenic concentration was 500 µg/litre (village averages varying between 54 and 831 µg/litre); approximately 50% were between 400 and 700 µg/litre. In a survey (1964-1966) of the arsenic concentration in artesian wells in the BFD-endemic area, a total of 114 wells were studied; the arsenic concentration was between 10 and 1820 µg/litre, and more than 50% of the wells had a concentration between 300 and 700 µg/litre. Within a single village, the variation between individual wells was quite marked (10-700 µg/litre in one village and 200-900 µg/litre in another village). From national surveys performed in 1974-1976 it was concluded that in 29.1% of the wells, the arsenic concentration exceeded 50 µg/litre and in 5.2% it exceeded 350 µg/litre. The highest reported value for the BFD-endemic area was stated to be 2500 µg/litre. For the rest of Taiwan, 5% of wells had an arsenic concentration of 50 µg/litre or more, and 0.3% had 350 µg/litre or more. For Taiwan as a whole, the figures were 18.7% and 2.7%.
According to WHO (2001), the accuracy and sensitivity of the methods employed for the analysis of arsenic in the studies described above is not clear.

Historical records of arsenic concentrations in drinking-water were available for 1950-1992 in a region of Chile. The annual 'province-weighted average' water arsenic levels were approximately 200 µg/litre in the years 1950-1957, 650 µg/litre for 1958-1970, 200 µg/litre for 1971, 540 µg/litre for 1972-1977, 100 µg/litre for 1978-1987 and 50 µg/litre thereafter. There was a marked variation between the different locations within the region. There is no information on the number of measurements actually performed, or on the methods used.

The assessment of exposure in studies in Argentina was based on measurements in the 1930s, two scientific sampling studies, and one local water survey in the 1970s. In the 1930s survey, 42/61 and 49/57 measurements of arsenic in drinking-water were above the detection limit (40 µg/litre) in the two counties in the high-exposure group. The highest measured concentration was 533 µg/litre and the average drinking-water concentration of the measurements above 40 µg/litre in the two "high-exposure" counties was 178 µg/litre; the authors noted, however, that this should not be considered to be representative of the population exposure.

3.2.2 Dermal effects

One of the most common and characteristic effects of arsenic ingestion is a pattern of skin changes that include generalised hyperkeratosis and formation of hyperkeratotic warts or corns on the palms and soles, along with areas of hyperpigmentation interspersed with small areas of hypopigmentation on the face, neck, and back. These and other dermal effects have been noted in a large majority of human studies involving repeated oral exposure from different regions of the world where the content of arsenic in drinking water is elevated. In cases of low-level chronic exposure (usually from water), these skin lesions appear to be the most sensitive indication of effect. (ATSDR 2007, IARC 2004).

The lowest arsenic drinking-water concentration where an elevated risk of arsenic-associated skin lesions (hyperpigmentation and/or keratosis) has been found can be estimated from the study in West Bengal to be < 50 μg/litre (WHO 2001).

3.2.3 Vascular effects

The following summary is based primarily on WHO (2001).

Several studies in Taiwan have demonstrated an association between arsenic ingestion and "blackfoot disease" (BFD), with clear exposure-response effects related to both the well-water arsenic levels and duration of use of arsenic-contaminated drinking-water. Preclinical cases have also been identified in formerly exposed individuals, suggesting that the effects of arsenic ingestion can persist after exposure has declined or ceased. Several other studies and case reports of subjects exposed to arsenic from many sources, in countries other than Taiwan, document an association with peripheral vascular alterations. However, the extreme form and high prevalence of BFD found in Taiwan has not been reported in other parts of the world, and contributing factors, such as malnutrition or other concurrent exposures, may play a role in the pathophysiology of the disease.

Hypertension is associated with long-term exposure to arsenic, but this evidence is limited to cross-sectional studies, one occupational and two environmental (Taiwan and Bangladesh), all three of which found elevations in blood pressure with arsenic exposure. The two environmental studies demonstrated exposure-response relationships. It should be noted that although hypertension is not a very important cause of death itself, it is a major risk factor for other vascular diseases.

Several studies in Taiwan show a relationship between arsenic exposure and mortality from cardiovascular diseases (CVD), including exposure-response relationships. Similar results have generally not been observed in other arsenic drinking-water studies or in a medicinal study, in all of which the exposure levels have been lower. In the occupational studies, mortality from arteriosclerosis and coronary heart disease was elevated in the latest report from a cohort study in the USA (the Tacoma cohort), but no statistically significant increases for these effects have been found in the Ronnskar (Sweden) or Anaconda (USA) smelter cohorts. A study in Utah (USA) found an excess of mortality from hypertensive heart disease but there were only a small number of deaths.

Only very limited evidence exists for an association between arsenic exposure and cerebrovascular disease. Some of the Taiwanese studies have shown an elevated risk of death from cerebrovascular disease, but the data are inconsistent across studies and the elevations, where present, are small compared with those for CVD.

Studies from other countries provide only very limited support for the Taiwanese findings, but exposure levels were considerably lower.

3.2.4 Neurological effects

There is little evidence of neurological effects from long-term lower-level environmental or occupational exposure. The few published studies have suggested changes in peripheral nerve function after arsenic exposure, but the studies have been limited by small numbers, different methods used to assess the end-points and co-exposure to other known neurotoxins. (WHO 2001).

3.2.5 Liver effects

Exposure to inorganic arsenicals has been associated with the development of chronic pathological changes in the liver. Liver enlargement has been reported in cases of chronic arsenic toxicity caused by arsenic in drinking water, and analysis of blood sometimes has shown elevated levels of hepatic enzymes. (IARC 2004, ATSDR 2007).

3.2.6 Gastrointestinal disturbances

Chronic arsenic toxicity has been reported to produce various gastrointestinal symptoms such as gastroenteritis, dyspepsia, nausea, diarrhoea, anorexia and abdominal pain (IARC 2004, ATSDR 2007).

3.2.7 Chronic lung disease

The possible role of chronic ingestion of arsenic in non-malignant pulmonary disease has been suggested in a few case series describing medical problems among individuals chronically exposed to increased concentrations of arsenic in the drinking water (IARC 2004).

3.2.8 Diabetes mellitus

In Taiwan, the prevalence and mortality rates of diabetes mellitus were higher among the population of the BFD-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. Two occupational studies found an association of borderline statistical significance between diabetes mellitus and exposure to arsenic. (WHO 2001).

3.3 Toxicity to reproduction

Exposure to arsenic in drinking water has been associated with adverse reproductive outcomes (spontaneous abortions) in some studies.

Chronic exposure of women to arsenic in the drinking water has been associated with infants with low birth weights in Taiwan and Chile. Similar associations have

been made between late foetal mortality, neonatal mortality, and postnatal mortality and exposure to high levels of arsenic in the drinking water, based on comparisons between subjects in low- and high-arsenic areas of Chile. A more recent study (2006) reported no significant association between exposure to concentrations of ≥0.1 mg/L arsenic in drinking water and increased risk for neonatal death or infant mortality during the first year of life in a study of a population in West Bengal, India. No overall association between arsenic in drinking water and congenital heart defects was detected in a case-control study in Boston, although an association with one specific lesion (coarctation of the aorta) was noted. (ATSDR 2007, IARC 2004, WHO 2001).
According to WHO (2001), there is no consistent evidence for any one particular end-point.

3.4 Mutagenic and genotoxic effects

3.4.1 Human evidence

Genotoxicity studies in relation to arsenic exposure have included exposed and unexposed individuals from several populations, and have based their analysis on various tissues, including blood, buccal and bladder cells as well as sections from tumour biopsies or Bowen's disease.

Arsenic can cause clastogenic damage in different cell types, with different end-points, in exposed individuals. Clastogenic effects have also been observed in cells from cancer patients. Arsenic is thus clastogenic in humans *in vivo*. However, no HPRT gene mutation was seen in the single study in lymphocytes or increases in ras or p53 gene expression in cells from cancer or Bowen's disease patients with long-term exposure to arsenic, except for one study with increased p53 expression in Bowen's disease patients with such exposure compared to patients without exposure. For point mutations, the results are largely negative. (IARC 2004, WHO 2001, ATSDR 2007).

Table 3. Genotoxicity studies after arsenic exposure (WHO 2001)

Micronuclei	**Sister chromatid exchanges**	**Chromosome aberrations**	**Aneuploidy**	**HPRT mutation**	**P53 / ras expression**
Urinary epithelial cells	Lymphocytes	Lymphocytes	Lymphocytes	Lymphocytes	
+ （USA）	+ （Argentina）	−,+ （Mexico）	+ （Argentina）	− （Mexico）	− urothelial cancer patients （Taiwan）
+ （Chile）	− （Mexico）	+ （Mexico）			− Bowen's disease （Taiwan）
+ （Argentina）	− （Argentina）	± （Finland）			+ Bowen's disease （Taiwan）
Buccal cells	+ Bowen's disease （Taiwan）	+ cancer patients （Taiwan）			

- （USA）	- cancer patients, BFD （Taiwan）				
+ （Mexico）					

3.4.2 Experimental studies

There are a large number of studies on the genotoxic effects of inorganic arsenic. In general, *in vitro* studies in prokaryotes have been negative for gene mutations and arsenic is not considered to be a point mutagen in bacteria. Tests in mammalian cells (human fibroblasts lymphocytes and leukocytes, mouse lymphoma cells, Chinese hamster ovary cells, and Syrian hamster embryo cells) demonstrate that *in vitro* arsenic can induce chromosomal aberrations ad sister chromatid exchange and aneuploidy. *In vitro* tests in human, mouse, and hamster cells have also been positive for DNA damage and repair and enhancement or inhibition of DNA synthesis. *In vitro*, arsenite was genotoxic at micromolar concentrations. Arsenate was approximately one order of magnitude less genotoxic than arsenite.
In vivo studies have shown both positive and negative results for chromosomal aberrations in rat and mouse bone marrow cells following oral administration. One study in mice gave a positive result for micronuclei formation in bone marrow cells following intraperitoneal injection.
The genotoxicity of arsenic is due largely to the trivalent arsenicals.
In combination with many genotoxic agents, including ultraviolet light, arsenic was a synergistic co-mutagen.
(ATSDR 2007, IARC 2004).

3.5 Carcinogenic effects

Informative epidemiological studies of cancer in relation to arsenic in drinking-water include ecological studies and fewer case-control and cohort studies. For arsenic in drinking-water, ecological studies provide important information for causal inference. The reasons include large exposure contrasts and limited population migration. As a consequence of widespread exposure to local or regional water sources, ecological measurements provide a strong indication of individual exposure. Moreover, in the case of arsenic, the ecological estimates of relative risk are often so high that potential confounding with known causal factors cannot explain the results. (IARC 2004).

Long-term exposure to arsenic in drinking-water is causally related to increased risks of cancer in the skin, lungs, bladder and kidney. 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. (WHO 2001).

3.5.1 Cancer of the lung, bladder, and kidney

3.5.1.1 WHO (2001)

Studies in Taiwan, Chile and Argentina show consistently high mortality risks from lung, bladder and kidney cancer among populations exposed to arsenic via drinking-water. Where exposure-response relations have been studied, the risk of cancer for these sites increases with increasing exposure. Even when tobacco smoking has been considered, the exposure-response relationship remains.

Not all studies of populations exposed to arsenic have reported positive findings for increased lung, bladder and kidney cancer. According to WHO (2001), exposure in these studies have not been as high as those in Taiwan, Chile or Argentina, and the sample sizes of the study populations may not have provided the statistical power to detect increased risks.

Studies on populations occupationally exposed to arsenic by inhalation, such as smelter workers, pesticide manufacturers and miners in many different countries, consistently demonstrate an excess lung cancer risk among the arsenic-exposed. Although all these groups are exposed to other chemicals in addition to arsenic, it is unlikely that some other common factor could explain the findings. The lung cancer risk increases with increasing arsenic exposure in all studies where exposure-response relationships have been investigated. Tobacco smoking has been investigated in several studies in two of the three main smelter cohorts, and was not found to be the cause of the increased lung cancer risk attributed to arsenic; however, it was found to be interactive with arsenic in increasing the lung cancer risk.

Risks of kidney or bladder cancer are not consistently elevated in studies among people occupationally exposed to arsenic by inhalation. According to WHO (2001), this difference between the occupational and environmental studies may reflect lower systemic concentrations of arsenic after inhalation exposure than after oral exposure.

According to WHO (2001), it is difficult to determine the lowest arsenic drinking-water concentration at which increased risks of lung, bladder and kidney cancer may be found. Most of the studies where these effects have been observed were conducted in Taiwan. The exposure categories of studies conducted in the BFD-endemic area in Taiwan have historically been rather broad (e.g., < 300 µg/litre, 300-600 µg/litre, and > 600 µg/litre). A recent paper on the BFD-endemic area in Taiwan, however, reported increased risks of bladder and lung cancer mortality in persons consuming drinking-water with arsenic concentrations < 50 µg/litre. There is a footnote in WHO (2001) stating that while this EHC was in the press, a cohort study from north-eastern Taiwan also reported an exposure-dependent increase in the risk of bladder cancer in exposure categories 10-50, 50-100, and > 100 µg/litre. Unlike all earlier Taiwanese studies, this study used estimates of individual (rather than village average) drinking-water arsenic concentrations, and incidence rather than mortality as the end-point. Arsenic measurements in the well-water were performed using a hydride-generation atomic absorption method, and the results were adjusted for age, sex and cigarette smoking.

In Argentina, significantly elevated bladder, lung and kidney cancer mortality were found in the high-exposure group where over 75% of the measurements of arsenic in drinking-water were higher than the detection limit of 40 µg/litre. For the measurements over the detection limit, the average concentration was 178 µg/litre, which, according to WHO (2001), can be taken as the lowest exposure where these

effects are observed. Exposure concentrations were not provided for the low- or intermediate-exposure groups although bladder, lung and kidney cancer mortality were significantly elevated for men and lung cancer mortality was significantly elevated for women in the intermediate-exposure group. Thus, according to WHO (2001), the lowest exposure where elevated kidney cancer risk could be observed would have to be considerably lower than 178 µg/litre.

In a case-control study conducted in Chile, there was an exposure-response relationship for the risk of lung cancer over all exposure categories, and the increased risk was statistically significant at exposures of 30-50 µg/litre and above.

In a case-control study in Finland, a statistically significantly elevated risk of bladder cancer was observed at ≥ 0.5-64 µg As/litre drinking-water concentration but only when exposure was 3-9 years before diagnosis.

3.5.1.2 IARC (2004)

The Working Group evaluated ecological studies in Taiwan (China), Chile, Argentina and Australia, cohort studies from Taiwan, Japan (bladder, lung) and the USA, and case-control studies in Taiwan (bladder, lung), the USA (bladder), Chile (lung) and Finland (bladder).

There is extensive evidence of increased risks for urinary bladder cancer associated with arsenic in drinking-water. All studies that involved populations with high long-term exposures found substantial increases in the risk for bladder cancer. Key evidence derives from ecological studies in Taiwan and Chile. In Taiwan, the evidence is supported by case-control studies and cohort studies within the exposed communities that demonstrate evidence of dose-response relationships with levels of arsenic in drinking-water. The evidence of increased mortality from bladder cancer in Chile comes from a large population with exposure to arsenic in all major cities and towns of the contaminated region.
There is also evidence of increased risks for bladder cancer from a small cohort study in Japan of persons drinking from wells that had been highly contaminated with arsenic wastes from a factory and an ecological study from Argentina with moderate exposure to arsenic in well-water. Two case-control studies that investigate low exposure to arsenic found increased risks with increasing exposure in one or more subgroups.
Considered overall, the findings cannot be attributed to chance or confounding, and they are consistent, with strong associations found in populations with high exposure. There is evidence of dose-response relationships within exposed populations.

Increased risk for lung cancer was consistently observed in ecological, case-control and cohort studies in Taiwan, Japan, Chile and Argentina. Evidence for a dose-response relationship between arsenic in drinking-water and risk for lung cancer was also observed in ecological studies in Taiwan and Argentina, in cohort studies in south-western and north-eastern Taiwan and Japan and in case-control studies in south-western Taiwan and Chile. The potential confounding effect of cigarette smoking was ruled out by direct and indirect evidence in studies from Taiwan and Chile.
Considered overall, the findings cannot be attributed to chance or confounding, are consistent and demonstrate strong associations in populations with high exposure. There is evidence of a dose-response relationship.

All studies that involved populations with high long-term exposures to arsenic found increased risks for kidney cancer. Key evidence comes from ecological studies in Taiwan and Chile. In Taiwan, the evidence is supplemented by a small cohort study of patients with Blackfoot disease. The evidence of increased mortality from kidney cancer in Chile comes from a large population with exposure to arsenic in all major cities and towns of the region. There is also evidence of increased risk for kidney cancer in populations in Argentina with moderate exposure to arsenic in well-water.
Relative risk estimates for kidney cancer were generally lower than those for urinary bladder cancer, and no studies have reported dose-response relationships on the basis of individual exposure assessment.

3.5.2 Cancer of the skin

3.5.2.1 WHO (2001)

Arsenic ingestion in drinking-water has been shown to be associated with a high risk of skin cancer. Well-documented studies on skin cancer after arsenic ingestion from drinking-water have been conducted in several populations in different countries, the largest of which were in Taiwan. Association of exposure to arsenic with skin cancer has also been observed in studies on patients treated with arsenicals.

The lowest arsenic drinking-water concentration where an increased risk of skin cancer could be observed is in the lowest exposure group in the exposed Taiwan population (i.e., < 300 µg/litre). It should be noted, according to WHO (2001), that this is a very broad exposure category and the lowest concentration associated with skin cancer could have been considerably lower.

The lowest arsenic drinking-water concentration where an elevated risk of arsenic-associated skin lesions (hyperpigmentation and/or keratosis) has been found can be estimated from the study in West Bengal to be less than 50 µg/litre.

3.5.2.2 IARC (2004)

The Working Group evaluated ecological studies from Taiwan (China), Mexico, Chile and the USA, cohort studies from Taiwan and a case-control study from the USA.

The recognition that arsenic was potentially carcinogenic arose from occurrences of skin cancer after ingestion of medicinal arsenic, arsenical pesticide residues and arsenic-contaminated drinking-water. Skin cancer is a commonly observed malignancy related to contamination of drinking-water with arsenic. The characteristic arsenic-associated skin tumours include keratinocytic malignancies (non-melanoma skin cancers), in particular squamous-cell carcinomas, including Bowen disease, and multiple basal-cell carcinomas.

Ecological studies, largely from the south-west of Taiwan, indicate substantially elevated incidence of, prevalence of and mortality rates for skin cancer associated with drinking-water highly contaminated with arsenic, with evidence of a dose-response relationship. Findings in ecological studies were substantiated in two cohort studies in the region of Taiwan that is endemic for arsenic. Increased mortality from skin cancer was found in Chile. A high prevalence of skin lesions, including skin cancers, was found in rural regions of Mexico. An excess risk for skin cancer was observed in a case-control study in the USA conducted in an area with lower concentrations of arsenic in drinking-water. A cohort study from the

south-west of Taiwan reported that differences in the levels of serum beta-carotene and urinary arsenic metabolites may modify the risk for arsenic-induced skin cancers.

3.5.3 Cancer at other sites

3.5.3.1 WHO (2001)

In two partly overlapping studies in Taiwan, an elevated mortality from liver cancer was observed in relation to arsenic exposure from drinking-water. In one of the two studies in Chile, but not in the study in Argentina, such a relationship was observed.

Cancer at other sites in relation to arsenic exposure has been little studied outside Taiwan. The sites that have exhibited an elevated risk include oesophagus, stomach, small intestine, colon, nose, larynx, bone and prostate, as well as lymphoma and leukaemia. A study in the USA and another in Australia, neither of which showed a clear-cut increase in the risk of lung, bladder, or kidney cancer, showed moderately elevated mortality from cancer of the prostate. The studies on occupational exposure of arsenic have not found any consistent relationship between exposure to arsenic and cancer at sites other than lung.

3.5.3.2 IARC (2004)

The Working Group evaluated ecological studies using mortality data in Taiwan (China), Chile, Argentina and Australia, cohort studies in Taiwan, Japan and the USA and a case-control study in Taiwan of liver cancer cases identified from death certificates.
Increased mortality from liver cancer was observed in the ecological studies involving a large population with high exposure to arsenic in Taiwan. Evidence for a dose-response relationship between arsenic in drinking-water and liver cancer mortality was observed in both ecological and case-control studies in Taiwan. Increased risks were also found in small cohort studies in Taiwan and Japan. Findings on mortality from liver cancer observed in ecological studies in Chile are inconsistent.
The interpretation of these findings is limited by the small number of liver cancer cases, questionable accuracy of the diagnosis of liver cancer on death certificates and potential confounding or modifying effects of chronic hepatitis virus infection or other factors.

The Working Group evaluated ecological studies from Taiwan (China), Chile and the USA, cohort studies from Japan and the USA and one case-control study each from Canada and the USA.
Excess mortality from prostate cancer was found in south-west Taiwan. nconsistent findings were reported for other cancer sites.

3.5.4 Conclusion WHO and IARC

3.5.4.1 WHO (2001)

Long-term exposure to arsenic in drinking-water is causally related to increased risks of cancer in the skin, lungs, bladder and kidney. 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. 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 As/litre.

It cannot be stated with certainty that arsenic exposure causes cancer at sites other than lung, skin, kidney and bladder. It is apparent that if such a causality exists, the relative risk of cancer at such sites must be lower than that for the sites for which the causality has been demonstrated.

3.5.4.2 IARC (2004)

There is sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin (Group 1).

3.5.4.3 IARC (2009)

In March, 2009, the IARC Working Group met to reassess the carcinogenicity of a number of compounds previously classified as "carcinogenic to humans" (Group 1) and to identify additional tumour sites and mechanisms of carcinogenesis. Arsenic was one of the compounds being evaluated. The following is an extract of a short 'Special Report' from the meeting (Straif et al. 2009): "*Non-occupational exposure to arsenic is mainly through food, except in areas with high levels of arsenic in the drinking water, e.g., Taiwan, Bangladesh, West Bengal (India), northern Chile, and Cordoba Province (Argentina). Epidemiological studies have shown that exposure to arsenic through inhalation or drinking-water causes cancer of the lung, skin, and urinary bladder. Evidence suggests an association between exposure to arsenic in drinking water and the development of tumours at several other sites; however, various factors prevent a conclusion. Analytical studies have provided only limited information to support an association with kidney cancer, causes of liver cancer can be difficult to elucidate in groups that are high-risk for hepatitis B, and data on prostate cancer and arsenic exposure are not consistent between countries. Overall, the Working Group classified arsenic and inorganic arsenic compounds as "carcinogenic to humans" (Group 1).*"
Established mechanistic events include "*Oxidative DNA damage, genomic instability, aneuploidy, gene amplification, epigenetic effects, DNA-repair inhibition leading to mutagenesis.*"
The assessments will be published as part C of Volume 100 of the IARC Monographs.

3.5.5 Danish study

In a recent Danish study, Baastrup et al. (2008) examined whether exposure to low levels of arsenic in drinking-water in Denmark was associated with an increased risk for cancer. The study was based on a prospective Danish cohort of 56,378 persons in the Copenhagen and Aarhus areas. Cancer cases were identified in the Danish Cancer Registry, and the Danish civil registration system was used to trace and geocode residential addresses of the cohort members. A geographic information system was used to link addresses with water supply areas, then estimated individual exposure to arsenic using residential addresses back to 1970. Average exposure for the cohort ranged between 0.05 and 25.3 µg/litre (mean: 1.2 µg/litre). Cox's regression models were used to analyse possible relationships between arsenic and cancer. No significant association between exposure to arsenic

and risk for cancers of the lung (402 cases), bladder (214 cases), liver (35 cases), kidney (53 cases), prostate (332 cases), or colorectum (441 cases), or melanoma skin cancer (147 cases) was found. The risk for non-melanoma skin cancer (1010 cases) decreased with increasing exposure (incidence rate ratio: 0.88/µg/litre average exposure; 95% confidence interval, 0.84-0.94). Results adjusted for enrolment area showed no association with non-melanoma skin cancer. The authors concluded: "*The results indicate that exposure to low doses of arsenic might be associated with a reduced risk for skin cancer. The results also indicated that arsenic in drinking-water might increase the risk for breast cancer* (766 cases). *The findings should be interpreted with caution, and more studies are needed to confirm the results.*"

4 Animal toxicity

Both inorganic and organic forms of arsenic may cause adverse effects in laboratory animals. The effects induced by arsenic range from acute lethality to chronic effects such as cancer. The degree of toxicity of arsenic is basically dependent on the form (e.g. inorganic or organic) and the oxidation state of the arsenical. It is generally considered that inorganic arsenicals are more toxic than organic arsenicals, and within these two classes, the trivalent forms are more toxic than the pentavalent forms, at least at high doses. Several different organ systems are affected by arsenic, including skin, respiratory, cardiovascular, immune, genitor-urinary, reproductive, gastro-intestinal and nervous systems. (WHO 2001).

The toxicological effects exerted by arsenic are similar in humans and in experimental animals. However, the available data indicate that most laboratory animals appear to be substantially less susceptible to the toxicity of inorganic arsenic than humans. This might be due to the pronounced interspecies differences in the metabolism of arsenic. Moreover, while there is sufficient evidence that arsenic in drinking water is carcinogenic to humans, the evidence of carcinogenicity in animals is mostly negative. IARC (2004) has concluded that, taken together, the studies on inorganic arsenic provide limited evidence for carcinogenicity in experimental animals. For these reasons, data from studies in laboratory animals are not included in this evaluation.

5 Regulations

5.1 Ambient air

Denmark (C-value): 0.00001 mg As/m^3, inorganic arsenic, Main Group 1 (MST 2002).

5.2 Drinking water

Denmark: 10 µg As/litre (MM 2001).

EU: 10 µg As/litre (OJ 1998).
A planned revision of the drinking water directive 98/83/EC has been postponed (NST 2011).

WHO: 10 µg/litre, provisional (WHO 2003).

The background for the provisional guideline value is as follows (WHO 2003):
"The concentration of arsenic in drinking-water below which no effects can be observed remain 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 end-point. The practical quantification limit for arsenic is in the region of 1-10 µg/litre, and removal of arsenic to concentrations below 10 µg/litre is difficult in many circumstances. In view of the significant uncertainties surrounding the risk assessment for carcinogenicity and the practical difficulties in removing arsenic from drinking-water, the guideline value of 10 µg/litre is retained. In view of the scientific uncertainties, the guideline value is designated as provisional. 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."

In the previous version of the WHO Guidelines for drinking-water quality (WHO 1996), the background for the provisional guideline value of 10 µg/litre is as follows:
"A value of 13 µg/litre may be derived (assuming a 20% allocation to drinking-water) on the basis of the provisional maximum tolerable daily intake (PMTDI) of inorganic arsenic of 2 µg/kg bw set by the Joint FAO/WHO Expert Committee of Food Additives (JECFA) in 1983 and confirmed as a provisional tolerable weekly intake (PTWI) of 15 µg/kg bw in 1988. JECFA noted, however, that the margin between the PTWI and intakes reported to have toxic effects in epidemiological studies was narrow. With a view to reducing the concentration of arsenic in drinking-water, a provisional guideline value of 0.01 mg/litre is recommended. The estimated excess lifetime risk of skin cancer associated with exposure to this concentration is 6 x 10^{-4}."
The background for the JECFA PMTDI/PTWI is given in section 5.9.

US-EPA: 10 µg/litre (US-EPA 2001).

5.3 Soil

Denmark: 20 mg As/kg soil (MST 1995).

5.4 Occupational Exposure Limits

Denmark: 0.01 mg As/m^3, arsenic and inorganic arsenicals except arsine and calcium arsenate, notation K, (1996) (At 2007).

5.5 Classification

Both the classification according to the Dangerous Substances Directive 67/548/EEC (DSD) in the former chemical regulation as well as the classification according to the present CLP-Regulation (EC) No 1272/2008 (CLP: Classification, Labelling and Packaging) are reproduced from the European chemical Substances Information System (ESIS 2011):

Arsenic (element):
DSD: T;R23/25, N;R50/53
CLP: Acute Tox. 3 H331, Acute Tox. 3 H301, Aquatic Acute 1 H400, Aquatic Chronic 1 H410

Arsenic trioxide, diarsenic trioxide:
DSD: Carc. Cat. 1;R45, Tx;R28, C;R34, N;R50/53
CLP: Carc 1A H350, Acute Tox. 2 H300, Skin Corr. 1B H314, Aquatic Acute 1 H400, Aquatic Chronic 1 H410

Diarsenic pentaoxide, arsenic oxide, arsenic pentoxide:
DSD: Carc. Cat. 1;R45, T;R23/25, N;R50/53
CLP: Carc 1A H350, Acute Tox. 3 H331, Acute Tox. 3 H301, Aquatic Acute 1 H400, Aquatic Chronic 1 H410

Arsenic acid and its salts, with the exception of those specified elsewhere in the Annex:
DSD: Carc. Cat. 1;R45, T;R23/25, N;R50/53
CLP: Carc 1A H350, Acute Tox. 3 H331, Acute Tox. 3 H301, Aquatic Acute 1 H400, Aquatic Chronic 1 H410

Arsenic compounds, with the exception of those specified elsewhere in the Annex:
DSD: T;R23/25, N;R50/53
CLP: Acute Tox. 3 H331, Acute Tox. 3 H301, Aquatic Acute 1 H400, Aquatic Chronic 1 H410

5.6 IARC

Arsenic in drinking-water is carcinogenic to humans (Group 1). There is sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin. Taken together, the studies on inorganic arsenic provide limited evidence for carcinogenicity in experimental animals. (IARC 2004).

This conclusion was reaffirmed at an IARC Working Group meeting in March 2009: "*Overall, the Working Group classified arsenic and inorganic arsenic compounds as "carcinogenic to humans" (Group 1).*" (Straif et al. 2009).

5.7 US-EPA

Maximum Contaminant Level (MCL): 0.010 mg/litre (US-EPA 2001).

Oral reference dose (RfD): 0.0003 mg/kg bw/day (last revised: 02/01/1993).
The oral RfD is based on a NOAEL of 0.0008 mg/kg bw/day for hyperpigmentation, keratosis and possible vascular complications in humans following chronic oral exposure (data from the BFD endemic area of Taiwan). An uncertainty factor of 3 is applied "*to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals*".
The background for the NOAEL is as follows:
"*NOAEL was based on an arithmetic mean of 0.009 mg/litre in a range of arsenic concentration of 0.001 to 0.017 mg/litre. This NOAEL also included estimation of arsenic from food. Since experimental data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 litre water/day and 55 kg body weight. NOAEL = [(0.009 mg/litre x 4.5 litre/day) + 0.002 mg/day] / 55 kg = 0.0008 mg/kg bw/day. The LOAEL dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from of 0.17 mg/litre. LOAEL = [(0.17 mg/litre x 4.5 litre/day) + 0.002 mg/day] / 55 kg = 0.014 mg/kg bw/day*." (IRIS 2008).

Carcinogenicity: Group A, human carcinogen, (last revised: 04/10/1998).
The basis is as follows:
"*There is sufficient evidence from human data. An increased lung cancer mortality was observed in multiple human populations exposed primarily through inhalation. Also, increased mortality from multiple internal organ cancers (liver, kidney, lung, and bladder) and an increased incidence of skin cancer were observed in populations consuming drinking water high in inorganic arsenic.*" (IRIS 2008).

The US-EPA has recently (February 2010) released a 'Toxicological Review of Inorganic Arsenic. The review is an external review draft and cannot be cited or quoted. (US-EPA 2011).

5.8 Office of Environmental Health Hazard Assessment, California EPA

The Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency has developed a Public Health Goal (PHG) of 0.004 µg/litre (4 ppt) for arsenic in drinking water.
According to the OEHHA Fact Sheet (OEHHA 2004b) "*A PHG is the level of a chemical contaminant in drinking water that, based upon currently available data, does not pose a significant risk to health. It represents an optimal level that the state's drinking water providers should strive to achieve if it is possible to do so. State law requires DHS*[2] *to set regulatory drinking water standards as close to the corresponding PHGs as is economically and technically feasible.*"

The background is as follows:

[2] The California Department of Health Services (DHS)

"*This risk assessment has derived a PHG of 4 ppt based on a unit risk of $2.7x10^{-4}$ $(\mu g/L)^{-1}$ and a negligible theoretical lifetime cancer risk level of $1x10^{-6}$. The unit risk was based on linear regression analysis of lung and urinary bladder cancer mortality data in epidemiological studies in Taiwan, Chile, and Argentina and background mortality rates for these cancers in the United States. Other estimates of unit risks include: $2.6x10^{-4}$ $(\mu g/L)^{-1}$ based on California mortality rates; $3.1x10^{-4}$ $(\mu g/L)^{-1}$ based on the sum of lung, bladder, skin, and kidney cancer mortality; and $5.9x10^{-4}$ $(\mu g/L)^{-1}$ based on lung and bladder cancer incidences rather than mortality. Unit risk estimates based on a transplacental carcinogenicity assay in mice were generally in the $1x10^{-4}$ to $1x10^{-3}$ $(\mu g/L)^{-1}$ range for various tumors and dose averaging methods. Thus the range of plausible PHGs based on these unit risks is 1.7 to 3.8 ppt. The latter figure rounded to one significant figure is considered the most robust estimate in this assessment.*" … "*The risk estimates were based on a low-dose linear extrapolation approach although the mode of carcinogenic action is not fully understood. The actual risks of low-level exposure are unlikely to exceed these risk estimates but could be lower or zero.*" (OEHHA 2004a).
Exposure to arsenic at the PHG level in drinking water results in a risk of less than one additional case of these forms of cancer in a population of one million people drinking two liters daily of the water for 70 years. While the PHG is based primarily on data from cancer studies, no other adverse health effects are expected to arise from arsenic at the level of the PHG." (OEHHA 2004b).

The OEHHA has to set the MCL as close as possible to the PHG, while considering cost and technical feasibility. Based on a cost-benefit analysis, an arsenic MCL in conformance with the federal MCL of 0.010 mg/litre was adopted. (OEHHA 2008).

5.9 WHO / JECFA

0.002 mg/kg bw, as a provisional maximum tolerable daily intake (PMTDI) for ingested inorganic arsenic (JECFA 1983).
0.015 mg/kg bw, provisional tolerable weekly intake (PTWI) (JECFA 1988). This PTWI was withdrawn in 2010, see below.

The rationale for the PMTDI is not expressed in JECFA (1983) except that it is stated "*On the basis of the data available, the Committee could arrive at only an estimate of 0.002 mg/kg bw as a provisional maximum tolerable daily intake (PMTDI) for ingested inorganic arsenic*". The data have been summarised as follows:
"*The available epidemiological evidence allows the tentative conclusion that arsenicism can be associated with water supplies containing an upper arsenic concentration of 1 mg/l or greater, and concentration of 0.1 mg/l may give rise to presumptive signs of toxicity. The chemical species of arsenic present in the drinking-water were not clearly determined but it would be reasonable to consider them to be inorganic arsenic. Assuming a daily water consumption of 1.5 litres (by no means an extreme figure), it seems likely that intakes of 1.5 mg/day of inorganic arsenic are likely to result in chronic arsenic toxicity and daily intakes of 0.15 mg may also be toxic in the long term to some individuals. In addition the use of arsenical pesticides may increase the exposure to inorganic arsenic by the oral route, in some individuals. Oral treatment of patients with solutions of inorganic arsenic is likely to result in intakes at least as great as those from arsenical water supplies. There are insufficient data to recommend a maximum tolerable daily intake for arsenic from food.*"

The rationale for the PTWI is not expressed in JECFA (1988) except that it is stated "*The previous evaluation was confirmed by assigning a PTWI of 0.015 mg/kg bw for inorganic arsenic, with the clear understanding that the margin between the PTWI and intakes reported to have toxic effects in epidemiological studies was narrow. The provisional status of the maximum weekly intake was continued due to the desire to lower the arsenic intake of those individuals exposed to high levels of inorganic arsenic in drinking water. Further epidemiological studies were recommended in such populations.*"

In their seventy-second meeting (February 2010), JECFA re-evaluated arsenic. The inorganic arsenic lower limit on the benchmark dose for a 0.5% increased incidence of lung cancer ($BMDL_{0.5}$) was determined from epidemiological studies by using a range of assumptions to estimate exposure from drinking water and food, with differing concentrations of inorganic arsenic. The $BMDL_{0.5}$ was computed to be 3.0 µg/kg bw per day (2-7 µg/kg bw per day based on the range of estimated total dietary exposure). The Committee noted that the PTWI of 15 µg/kg bw (2.1 µg/kg bw per day) is in the region of the $BMDL_{0.5}$ and therefore was no longer appropriate. The Committee withdrew the previous PTWI. (JECFA 2010).

5.10 European Food Safety Authority (EFSA)

The CONTAM Panel in EFSA (EFSA 2009) has noted that since the JECFA evaluations (before the JECFA 2010 re-evaluation), the IARC has concluded that there is sufficient evidence that arsenic in drinking water causes cancers in humans of the urinary bladder and lung as well as skin and that this conclusion was repeated in 2009, when an IARC working group also noted that there is limited evidence in humans for cancers of the kidney, liver and prostate. From the evidence relating to internal cancers and the studies showing statistically significant associations between adverse effects of arsenic and drinking water concentrations below 100 µg/litre, the CONTAM Panel concluded that the JECFA PTWI of 15 µg/kg bw for inorganic arsenic is no longer appropriate and, in its assessment, therefore focussed on more recent data showing effects of inorganic arsenic at lower levels of exposure than those considered by JECFA (before the JECFA 2010 re-evaluation).
The CONTAM Panel modelled the dose-response data from key epidemiological studies and selected a benchmark response of 1% extra risk. A range of benchmark doses lower confidence limit ($BMDL_{01}$) values between 0.3 and 8 µg/kg bw/day was identified for cancers of the lung, skin and bladder, as well as skin lesions. The CONTAM Panel noted that inorganic arsenic is not directly DNA-reactive and there are a number of proposed mechanisms of carcinogenicity, for each of which a thresholded mechanism could be postulated. However, taking into account the uncertainty with respect to the shape of the dose-response relationships, it was not considered appropriate to identify from the human data a dose of inorganic arsenic with no appreciable health risk, i.e., a tolerable daily or weekly intake. Therefore the margins of exposure (MOEs) should be assessed between the identified reference points from the human data and the estimated dietary exposure to inorganic arsenic in the EU population.
The estimated dietary exposures to inorganic arsenic for average (0.13-0.56 µg/kg bw/day) and high level adult consumers (0.37-1.22 µg/kg bw/day) in Europe are within the range of the $BMDL_{01}$ values (0.3-8 µg/kg bw/day) identified for lung and bladder cancer and for dermal lesions. Therefore there is little or no MOE and the possibility of a risk to some consumers cannot be excluded.

5.11 Scientific Committee on Health and Environmental Risks (SCHER)

SCHER has published an opinion for a derogation request of up to 50 μg/litre for arsenic in drinking water (the Drinking Water Directive's limit value for arsenic is 10 μg/litre). SCHER concluded that a derogation for drinking water containing up to 50 μg/litre for arsenic for up to 3 years does not result in or, at most, very low additional health risks in the adult population. The evaluation is based on the recent EFSA assessment of arsenic contamination of food (EFSA 2009, described in Section 5.10) and a number of recent large-scale epidemiology studies. It should be noted that a minority opinion was agreed by two members of SCHER as, for children up to 18 years and non-breast-fed infants, considering at least their comparatively higher intake, the risks are higher. The major concern is in particular for arsenic levels greater than 20 μg/litre. (SCHER 2010).

6 Summary and evaluation

6.1 Description

Arsenic can exist in four oxidation states: -3, 0, +3 and +5. In water, arsenic is mostly found in inorganic forms as oxyanions of trivalent arsenite (AsIII) or pentavalent arsenate (AsV). Under oxidising conditions, arsenate is dominant whereas, under reducing conditions, it is more likely to be present as arsenite.

In this evaluation, only soluble inorganic arsenic compounds are considered in relation to an estimation of a health-based quality criterion in drinking water.

6.2 Environment

Arsenic is naturally present in the earth's crust and is released to the environment from natural processes as well as from anthropogenic activities.

Three major modes of arsenic biotransformation have been found to occur in the environment: redox transformation between arsenite and arsenate, the reduction and methylation of arsenic, and the biosynthesis of organoarsenic compounds. There is biogeochemical cycling of compounds formed from these processes.

In water, inorganic arsenic occurs primarily in two oxidation states, pentavalent (arsenate) and trivalent (arsenite). Both forms generally co-exist, although arsenate predominates under oxidising conditions and arsenite predominates under reducing conditions.
Arsenic levels in groundwater worldwide average about 1-2 µg/litre except in areas with volcanic rock and sulphide mineral deposits where arsenic levels can range up to 3 mg/litre.
In Denmark (2006), the concentration of arsenic ranged from 0-3.75 µg/litre in 557/686 groundwater samples, from 3.75-5 µg/litre in 29/686 samples, and >5 µg/litre in 100/686 samples. In the period 1993-2006 (5140 groundwater samples), a mean concentration of 3.20 µg/litre was reported with a maximum value of 120 µg/l.
In Denmark (1991-2006), the concentration of arsenic in 83% of 4833 groundwater samples was below the limit value of 5 µg/litre. In 10% of the samples, the concentration was between 5 and 10 µg/litre, and in the remaining 7% of the samples, the concentration was above µg/litre. The median values from 2% of the samples showed a concentration of arsenic above 20 µg/litre.

Arsenic is found in the earth's crust at an average level of 2 mg/kg. Background concentrations in soil range from 1 to 40 mg/kg, with a mean of 5 mg/kg, although much higher levels may occur in mining areas, at waste sites, near high geological deposits of arsenic-rich minerals, or from pesticide application.
The concentration of arsenic in Danish soils was 3.3 As/kg (median) with the 95% percentile being 8.4 mg As/kg.
Two more recent projects concluded that the levels of arsenic found in urban areas correspond to the background level in country areas.

Arsenic is released into the atmosphere primarily as arsenic trioxide and exists mainly adsorbed on particulate matter. Typical background levels for arsenic in the atmosphere are 0.2-1.5 ng/m^3 for rural areas, 0.5-3 ng/m^3 for urban areas, and < 50 ng/m^3 for industrial sites.

Arsenic is found in many foods. In Denmark (1998-2003), arsenic was mainly found in marine foods with average concentrations in fish ranging from 352 to 10700 µg As/kg fresh weight. Average concentrations (µg As/kg fresh weight) in other foods were <5-56 (meat), 1-7 (dairy products), 0.5-8 (vegetables), about 20 (mushrooms), and 2-9 (beverages).

6.3 Human exposure

Non-occupational human exposure to arsenic in the environment is primarily through the ingestion of food and water, but contaminated ambient air and soil are also potential sources of exposure to arsenic. Of these sources, food is generally the principal contributor to the daily intake of total arsenic.

In Denmark, the mean intake of arsenic from the total diet (1998-2003) was estimated at 62 µg/day (0.9 µg/bw/day) for adults (15-75 years) with a 95th percentile of 227 µg/day (3.2 µg/bw/day). A vast majority of the intake (91% of the total intake) was from fish; however, inorganic arsenic levels in fish and seafood are generally low (< 1-10%).

Using the mean value for the concentration of arsenic in Danish groundwater of 3.2 µg As/l, the intake from drinking water would be 0.1 µg As/kg bw/day for children, and about 0.06 µg As/kg bw/day for adults.

Using the median value for the soil concentration of arsenic in Denmark of 3.3 mg As/kg soil, the intake from soil would be 0.03 µg As/kg bw/day for children 1-3 years old.

Using the upper value for the range of the typical background levels for arsenic in the atmosphere of 3 ng/m^3 for urban areas as a reasonable worst case scenario, the inhalation exposure to arsenic would be 1.5 ng As/kg bw/day for children, and about 0.6 ng As/kg bw/day for adults.

6.4 Toxicokinetics

The bioavailability of ingested inorganic arsenic will vary depending on the matrix in which it is ingested (e.g. food, water, beverages, soil), the solubility of the arsenical compound itself and the presence of other food constituents and nutrients in the gastrointestinal tract. Generally, soluble arsenic compounds are rapidly and well absorbed from the gastrointestinal tract in humans with between 45 and 75% of the dose of various inorganic forms of arsenic being excreted in the urine within a few days. Animal data indicate that up to 70-90% of an ingested dose of soluble inorganic arsenic is absorbed from the gastrointestinal tract when not administered in close proximity to feed.

Dermal absorption of inorganic arsenic in water is limited with absorption of about 2-6% depending on the dose level (absorption decreasing with increasing dose). For human skin *in vitro*, 1.9% was absorbed from water at a low dose over a 24-hour period.

After absorption, arsenic is rapidly cleared from blood in humans and in most common laboratory animals, including mice, rabbits, and hamsters, except the rat in which the presence of arsenic is prolonged due to accumulation in erythrocytes. Arsenic, administered orally, in either the trivalent or pentavalent form, is rapidly distributed throughout the body in humans and in laboratory animals and arsenic is generally present in all tissues. Skin, hair, nails, and tissues high in squamous epithelium (e.g. mucosa of the oral cavity, oesophagus, stomach and small intestine) have a strong tendency to accumulate and maintain higher levels of arsenic than other tissues.
Arsenic can cross the blood-brain barrier and it has been found in brain tissue after oral administration of trivalent or pentavalent inorganic arsenic; however, the levels are generally low.
Trivalent and pentavalent inorganic arsenic can cross the placenta in both humans and laboratory animals. Studies indicate that much of the arsenic reaching the foetus after oral administration has already been transformed to the less acutely toxic methylated metabolites.

Arsenic metabolism is via two main types of reactions: (1) reduction reactions of pentavalent to trivalent arsenic, and (2) oxidative methylation reactions in which trivalent forms of arsenic are sequentially methylated to form mono-, di- and trimethylated products. Methylation of inorganic arsenic facilitates the excretion of inorganic arsenic from the body, as the end-products MMA and DMA are readily excreted in urine.

Urine is the primary route of excretion for both pentavalent and trivalent inorganic arsenicals in most common laboratory animals as well as in humans. With the exception of the rat, which exhibits slower overall elimination of arsenic, 50% or more of a single oral dose of arsenic is usually eliminated in urine within 48 hours. Skin, hair and nails could also be considered potential excretory routes for arsenic, although they would in general be quantitatively minor. Arsenic can be excreted in human milk, although the levels are low.

There are pronounced interspecies differences in the elimination of arsenic. Most experimental animals excrete very little MMA in urine compared with humans. Some species, in particular guinea-pigs and several species of non-human primates (e.g. marmoset monkeys and chimpanzees) are unable to methylate inorganic arsenic at all whereas in humans and most common laboratory animals, inorganic arsenic is extensively methylated. In addition, rats show different kinetics of arsenic metabolism with a pronounced accumulation of DMAIII in red blood cells and greater biliary excretion of arsenic compared with humans.

There is also a wide inter-individual variation in the metabolism and excretion of arsenicals. Differences between population groups have also been reported. Data indicate that the influence of genetic polymorphism is more important than environmental factors for the variation in arsenic methylation.

6.5 Human toxicity

6.5.1 Acute toxicity

Inorganic arsenic is acutely toxic, and ingestion of large doses leads to gastrointestinal symptoms, disturbances of cardiovascular and central nervous system functions, multiorgan failure and eventually death. Lethal oral doses of 2-21 g (28-300 mg/kg bw) arsenic have been reported.

6.5.2 Chronic toxicity

Manifestations of chronic arsenic toxicity (chronic arsenicalism) include dermal effects, vascular diseases, neurological effects, liver effects, gastrointestinal disturbances, and chronic lung disease. Exposure to arsenic has also been associated with an increased risk for diabetes mellitus. These effects have been reported from different regions of the world where the content of arsenic in drinking-water is elevated.

6.5.3 Toxicity to reproduction

Limited human data suggest that exposure to high concentrations of arsenic in drinking-water during pregnancy may increase foetal, neonatal and postnatal mortality, lowered birth weight, spontaneous abortions, and congenital malformations. However, there is no consistent evidence for any one particular end-point.

6.5.4 Mutagenic and genotoxic effects

Although there are some negative findings, the overall weight of evidence indicates that arsenic can cause clastogenic damage in different cell types with different end-points in exposed individuals and in cancer patients. For point mutations, the results are largely negative.

In vitro, arsenic was not a point mutagen in bacteria. In mammalian cells *in vitro*, arsenic caused chromosomal aberrations ad sister chromatid exchange and aneuploidy. *In vitro* tests in human, mouse, and hamster cells have also been positive for DNA damage and repair and enhancement or inhibition of DNA synthesis. *In vitro*, arsenite was genotoxic at micromolar concentrations. Arsenate was approximately one order of magnitude less genotoxic than arsenite.
In vivo studies have shown both positive and negative results for chromosomal aberrations in rats and mice; one study gave a positive result for micronuclei formation in bone marrow cells of mice.
The genotoxicity of arsenic is due largely to the trivalent arsenicals.

6.5.5 Carcinogenic effects

Long-term exposure to arsenic in drinking-water is causally related to increased risks of cancer in the skin, lungs, bladder and kidney. 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 As/litre.

IARC (2004) has concluded that there is sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin. This conclusion was reaffirmed at the IARC Working Group meeting in March 2009.

In a recent Danish study (Baastrup et al. 2008), no significant association between exposure to arsenic in drinking water and risk for cancers of the lung, bladder, liver, kidney, prostate, or colorectum, or melanoma skin cancer was found. Average exposure for the cohort ranged between 0.05 and 25.3 µg/litre (mean: 1.2 µg/litre).

6.6 Animal toxicity

Inorganic arsenicals cause adverse effects in laboratory animals. The effects induced by arsenic range from acute lethality to chronic effects such as cancer. Several different organ systems are affected by arsenic, including skin, respiratory, cardiovascular, immune, genitor-urinary, reproductive, gastrointestinal and nervous systems.

The toxicological effects exerted by arsenic are similar in humans and in experimental animals. However, the available data indicate that most laboratory animals appear to be substantially less susceptible to the toxicity of inorganic arsenic than humans are.

IARC (2004) has concluded that, taken together, the studies on inorganic arsenic provide limited evidence for carcinogenicity in experimental animals.

6.7 Evaluation

The aim of this evaluation is to provide the most relevant information for the setting of a health-based quality criterion for inorganic arsenic in drinking water. Therefore, mostly information of relevance for this purpose has been considered and included in this evaluation. IARC (2004) has concluded that arsenic in drinking water is carcinogenic to humans (Group 1); this conclusion was reaffirmed in 2009 (Straif et al. 2009). Therefore, this endpoint is the main focus of this evaluation.

A variety of inorganic arsenates or arsenites occur in water, soil, or food. A number of studies have noted differences in the relative toxicity of these compounds, with trivalent arsenites tending to be somewhat more toxic than pentavalent arsenates. However, these distinctions have not been emphasised in this evaluation, for the following reasons: 1) In most cases, the differences in the relative potency are rather small (about 2-3-fold); 2) different forms of arsenic may be inter-converted, both in the environment and the body; and 3) in many cases of human exposure (especially those involving intake from water and soil), the precise chemical speciation is not known.

Inorganic arsenicals cause adverse effects in laboratory animals. The effects induced by arsenic range from acute lethality to chronic effects such as cancer. Several different organ systems are affected by arsenic, including skin, respiratory, cardiovascular, immune, genitor-urinary, reproductive, gastrointestinal and nervous systems.
The toxicological effects exerted by arsenic are similar in humans and in experimental animals. However, the available data indicate that most laboratory animals appear to be substantially less susceptible to the toxicity of inorganic arsenic than humans are. This might be due to the pronounced interspecies differences in the metabolism of arsenic. It is therefore difficult to evaluate human metabolism of arsenic based on much of the available experimental animal data. According to IARC (2004), hamsters and rabbits seem to be the most useful animal

species because their metabolism is most similar to that in humans; however, not much data are available regarding the toxicity of arsenics and no relevant carcinogenicity studies have been located. It is worth noting that IARC (2004) did not take rat data into account in their evaluation due to the species difference in toxicokinetics and metabolism between humans and rats. The data on human toxicity, including carcinogenicity are adequate in order to evaluate the toxicity of inorganic arsenics to humans. Therefore, only information on human toxicity is considered in this evaluation.

There is also a wide inter-individual variation in the metabolism and excretion of arsenicals. Differences between population groups have also been reported. Data indicate that the influence of genetic polymorphism is more important than environmental factors for the variation in arsenic methylation. This wide inter-individual variation has to be taken into account in the evaluation of human toxicity data.

Inorganic arsenic is acutely toxic in humans, and ingestion of large doses leads to gastrointestinal symptoms, disturbances of cardiovascular and central nervous system functions, multiorgan failure and eventually death. A precise estimate of the ingested dose is usually not available in acute poisonings, so quantitative information on lethal and non-lethal doses in humans is sparse. Lethal oral doses of 2-21 g (28-300 mg/kg bw) arsenic have been reported.

Manifestations of chronic arsenic toxicity (chronic arsenicalism) include dermal effects, vascular diseases, neurological effects, liver effects, gastrointestinal disturbances, and chronic lung disease. Exposure to arsenic has also been associated with an increased risk for diabetes mellitus. These effects have been reported from different regions of the world where the content of arsenic in drinking-water is elevated.
Extensive information concerning health effects of ingestion of inorganic arsenic in drinking-water comes from a series of studies performed in Taiwan. In the late 1960s, chronic arsenic exposure from drinking-water in Taiwan was suggested to be the cause of ”Blackfoot disease” (BFD), a severe form of PVD which leads to gangrenous changes. A significantly higher mortality from cardiovascular and peripheral vascular disease was reported among patients with BFD compared with the general population of Taiwan or unaffected residents in endemic areas of BFD. According to WHO (2001), BFD has not been documented in other parts of the world, and the findings in Taiwan may depend upon other contributing factors. However, there is good evidence from studies in several other countries that arsenic exposure causes other forms of PVD.
Conclusions on the causality of the relationship between arsenic exposure and other health effects are, according to WHO (2001), less clear-cut. The evidence is strongest for hypertension and cardiovascular disease, suggestive for diabetes and reproductive effects and weak for cerebrovascular disease, and long-term neurological effects.

Limited human data suggest that exposure to high concentrations of arsenic in drinking-water during pregnancy may increase foetal, neonatal and postnatal mortality, lowered birth weight, spontaneous abortions, and congenital malformations. However, there is no consistent evidence for any one particular end-point and, according to WHO (2001), the evidence is suggestive reproductive effects.

The overall weight of evidence from genotoxicity studies indicates that arsenic can cause clastogenic damage in different cell types with different end-points in

exposed individuals and in cancer patients. For point mutations, the results are largely negative.

Long-term exposure to arsenic in drinking-water is causally related to increased risks of cancer in the skin, lungs, bladder and kidney and IARC (2004) has concluded that there is sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin. This conclusion was reaffirmed at the IARC Working Group meeting in March 2009 (Straif et al. 2009). According to WHO (2001), it is difficult to determine the lowest arsenic drinking water concentration at which increased risks of lung, bladder and kidney cancer may be found. Most of the studies where these effects have been observed were conducted in Taiwan in which the exposure categories in the BFD-endemic area have been rather broad. However, a more recent paper on the BFD-endemic area reported increased risks of bladder and lung cancer mortality in persons consuming drinking water with arsenic concentrations < 50 µg/litre. In addition, a cohort study from Taiwan also reported an exposure-dependent increase in the risk of bladder cancer in exposure categories 10-50, 50-100, and > 100 µg/litre. This cohort study, unlike all earlier Taiwanese studies, used estimates of individual (rather than village average) drinking-water arsenic concentrations, and incidence rather than mortality as the end-point, and the results were adjusted for age, sex and cigarette smoking.
In a recent Danish study (Baastrup et al. 2008), no significant association between exposure to arsenic in drinking water and risk for cancers of the lung, bladder, liver, kidney, prostate, or colorectum, or melanoma skin cancer was found. Average exposure for the cohort ranged between 0.05 and 25.3 µg/litre (mean: 1.2 µg/litre).

6.7.1 Critical effect and NOAEL

Human exposure to inorganic arsenic via drinking water can result in a number of adverse health effects following intake of high doses as well as following much lower doses for a long time. Ingestion of large doses leads to gastrointestinal symptoms, disturbances of cardiovascular and central nervous system functions, multiorgan failure and eventually death. Manifestations of chronic toxicity include dermal effects, vascular diseases, neurological effects, liver effects, gastrointestinal disturbances, chronic lung disease, diabetes mellitus, reproductive effect, genotoxicity, and cancer. These effects have been reported from different regions of the world where the content of arsenic in drinking-water is elevated.

Long-term exposure to arsenic in drinking-water is causally related to increased risks of cancer in the skin, lungs, bladder and kidney and IARC (2004) has concluded that there is sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin; this conclusion was reaffirmed at the IARC Working Group meeting in March 2009 (Straif et al. 2009).

Inorganic arsenic is considered to be genotoxic in humans on the basis of clastogenicity in exposed individuals and findings *in vitro*.

According to WHO (WHO 2001), it is difficult to determine the lowest arsenic drinking water concentration at which increased risks of lung, bladder and kidney cancer (the most sensitive end-point) may be found. Drinking water concentrations of ≤ 50 µg As/litre (Taiwan) have been associated with increased risks of cancer in the bladder and lung and the most recent study in Taiwan reported an exposure-dependent increase in the risk of bladder cancer in exposure categories 10-50, 50-100, and > 100 µg/litre. The lowest arsenic drinking-water concentration where an

increased risk of skin cancer have been observed is in the lowest exposure group in the exposed Taiwan population (i.e., < 300 µg/litre); however, WHO noted that this is a very broad exposure category and the lowest concentration associated with skin cancer could have been considerably lower. Arsenic-associated skin lesions (precursors of skin cancer) have been associated with drinking water concentrations < 50 µg As/litre.

As inorganic arsenic in drinking water is carcinogenic to humans and causes genotoxic effects in humans (clastogenic damage in different cell types with different end-points in exposed individuals) it is considered, for the time being, that there is possibly no threshold for the carcinogenic effects, the most sensitive end-point. It should be noted, however, that the mechanism(s) by which arsenic causes cancer still remain to be fully elucidated. It should be noted that the IARC Working Group at their meeting in March 2009 (Straif et al. 2009) noted that established mechanistic events include oxidative DNA damage, genomic instability, aneuploidy, gene amplification, epigenetic effects, and DNA-repair inhibition leading to mutagenesis. It should also be noted that EFSA, in their very recent opinion (EFSA 2009), noted that inorganic arsenic is not directly DNA-reactive and there are a number of proposed mechanisms of carcinogenicity, for each of which a thresholded mechanism could be postulated.

The Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency has developed a Public Health Goal (PHG) of 0.004 µg/litre (4 ppt) for arsenic in drinking water. The PHG has been derived based on a unit risk of $2.7x10^{-4}$ $(\mu g/L)^{-1}$ and a negligible theoretical lifetime cancer risk level of $1x10^{-6}$. The unit risk was based on linear regression analysis of lung and urinary bladder cancer mortality data in epidemiological studies in Taiwan, Chile, and Argentina and background mortality rates for these cancers in the United States. It was noted that the risk estimate was based on a low-dose linear extrapolation approach although the mode of carcinogenic action is not fully understood. Exposure to arsenic at the PHG level in drinking water was stated to result in a risk of less than one additional case of these forms of cancer in a population of one million people drinking two liters daily of the water for 70 years. It was also noted that while the PHG is based primarily on data from cancer studies, no other adverse health effects are expected to arise from arsenic at the level of the PHG. (OEHHA 2004a,b).
In developing the PHG for arsenic, the OEHHA conducted an exhaustive analysis of available scientific studies on the health effects of arsenic. The risk assessment (OEHHA 2004a, 234 pages) and a Fact Sheet (OEHHA 2004b) were published in April 2004.

EFSA, in their recent opinion (EFSA 2009), stated that it was not considered appropriate to identify from the human data a dose of inorganic arsenic with no appreciable health risk, i.e., a tolerable daily or weekly intake. Therefore the margins of exposure (MOEs) should be assessed between the identified reference points from the human data and the estimated dietary exposure to inorganic arsenic in the EU population. EFSA selected the reference point as a benchmark response of 1% extra risk. A range of benchmark doses lower confidence limit ($BMDL_{01}$) values between 0.3 and 8 µg/kg bw/day was identified for cancers of the lung, skin and bladder, as well as skin lesions.

JECFA has very recently re-evaluated arsenic (JECFA 2010). The $BMDL_{0.5}$ for lung cancer was determined to be 3.0 µg/kg bw/day (2-7 µg/kg bw/day). As the previous PTWI of 15 µg/kg bw (2.1 µg/kg bw/day) is in the region of the $BMDL_{0.5}$, the Committee concluded that it was no longer appropriate and therefore, withdrew the PTWI.

SCHER has published an opinion for a derogation request of up to 50 µg/litre for arsenic in drinking water (the Drinking Water Directive's limit value for arsenic is 10 µg/litre). SCHER concluded that a derogation for drinking water containing up to 50 µg/litre for arsenic for up to 3 years does not result in or, at most, very low additional health risks in the adult population. It should be noted, however, that a minority opinion was agreed by two members of SCHER because, for children up to 18 years and non-breast-fed infants, the risks are higher. The major concern is in particular for arsenic levels greater than 20 µg/litre.

In the recent Danish study (Baastrup et al. 2008), no significant association between exposure to arsenic in drinking water and risk for cancers of the lung, bladder, liver, kidney, prostate, or colorectum, or melanoma skin cancer was found. Average arsenic exposure for the cohort ranged between 0.05 and 25.3 µg/litre (mean: 1.2 µg/litre).
The authors noted "*Although previous studies provide evidence for an etiologic relationship between arsenic in drinking-water and cancer, they do not predict the cancer risk of low doses.*" But they also noted "*Conflicting results have been obtained in studies of arsenic and cancer conducted in areas of low arsenic concentrations in drinking-water.*" It that respect, the authors claimed "*The arsenic levels in the Danish drinking-water are 100-1,000 times lower than those reported in studies from Asia and Latin America.*" And noted "*It is possible that arsenic concentrations in the Danish drinking-water are below a low effect level; however, the results of the present study cannot rule out a weak adverse effect that is impossible to detect with the method used and the study size.*"
The authors pointed out the strengths and limitations of the study: *"The strengths of our study include the large study population, the reliable population-based Danish registers, and adjustment for many potential confounding factors. Also, the precise link between place of residence and water supply and the measurements of arsenic concentrations in the drinking-water that was piped to the consumers adds strength to the study. The limitations of the study include the overall low arsenic concentration in Danish drinking-water and lack of information on other sources of arsenic. Further, the exposure of cohort members before 1970 could not be estimated, as the residential histories before that date were unknown. Therefore we were not able to assess early-life arsenic exposure, which is an important limitation of this study because early environmental exposures might be most significant for cancer risk. Finally, measurement of arsenic in nails or urine would provide more precise estimates of the personal exposure and should be included in future studies whenever possible."*

As inorganic arsenic in drinking water is carcinogenic to humans and causes genotoxic effects in humans, it is considered, for the time being, that there is possibly no threshold for the carcinogenic effects, the most sensitive end-point. In conclusion, the concentration of arsenic in drinking-water below which no effects can be observed cannot be determined for the time being and thus, a TDI / PTWI cannot be established for the critical effect(s).

7 Health-based quality criterion in drinking water

Inorganic arsenic in drinking water is carcinogenic to humans and causes genotoxic effects in humans. It is considered, for the time being, that there is possibly no threshold for the carcinogenic effects, the most sensitive end-point. Consequently, the concentration of arsenic in drinking-water below which no effects can be observed cannot be determined for the time being and thus, a TDI / PTWI cannot be established for the critical effect(s).

Various national and international bodies have published different estimates for the carcinogenic risks (as described in Chapter 5 and summarised in Section 6.7.1) and a consensus has not been arrived at yet.

The most relevant estimate for the carcinogenic risks of arsenic in drinking water is the unit risk of $2.7x10^{-4}$ $(\mu g/L)^{-1}$ developed by The Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency. Based on this unit risk, a Public Health Goal (PHG) of 0.004 µg/litre for arsenic in drinking water was established.
According to the OEHHA Fact Sheet (OEHHA 2004b) "*A PHG is the level of a chemical contaminant in drinking water that, based upon currently available data, does not pose a significant risk to health. It represents an optimal level that the state's drinking water providers should strive to achieve if it is possible to do so. State law requires DHS*[3] *to set regulatory drinking water standards as close to the corresponding PHGs as is economically and technically feasible.*"
It is noted in the Fact Sheet *"The PHG of 4 ppt for arsenic in drinking water is based upon lung and bladder cancer in studies of hundreds of thousands of people in communities in Taiwan, Chile, and Argentina associated with arsenic contaminated drinking water. Exposure to the PHG level in drinking water results in a risk of less than one additional case of these forms of cancer in a population of one million people drinking two liters daily of the water for 70 years. While the PHG is based primarily on data from cancer studies, no other adverse health effects are expected to arise from arsenic at the level of the PHG."*

The current limit value for arsenic in drinking water is 10 µg As/litre (MM 2001).

As inorganic arsenic in drinking water is carcinogenic to humans and causes genotoxic effects in humans, and as there is possibly no threshold for the carcinogenic effects, it is recommended that inorganic arsenic in drinking water should be as low as possible.

7.1.1 Health-based quality criterion in drinking water

It is recommended that inorganic arsenic in drinking water should be as low as possible.

[3] The California Department of Health Services (DHS)

8 References

At (2007). Grænseværdier for stoffer og materialer. Arbejdstilsynets At-vejledning C.0.1, August 2007.

ATSDR (2007). Toxicological Profile for Arsenic, Update. U.S. Department of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp2.html

Baastrup R, Sørensen M, Balstrøm T, Frederiksen K, Larsen CL, Tjønneland A, Overvad K and Raaschou-Nielsen O (2008). Arsenic in drinking-water and risk for cancer in Denmark. Environ Health Perspect **116**, 231-237.

BLST (2009). Arsen i dansk grundvand og drikkevand. Bind 1: Arsen i dansk grundvand. By- og Landskabsstyrelsen, Miljøministeriet.

DMU (1996). Tungmetaller i danske jorder. TEMA-rapport fra DMU, Miljø- og Energiministeriet, Danmarks Miljøundersøgelser 1996/4. http://www2.dmu.dk/1_viden/2_publikationer/3_temarapporter/rapporter/87-7772-235-3.pdf

EFSA (2009). Scientific opinion on arsenic in food. EFSA Panel on Contaminants in the food chain (CONTAM). European Food Safety Authority, adopted 12 October 2009. EFSA Journal 2009; 7(10): 1351 (198 pp.). Available online: www.efsa.europa.eu.

ESIS (2011): European chemical Substances Information System. http://esis.jrc.ec.europa.eu/index.php?PGM=cla

FDIR (2005). Food monitoring, 1998-2003, Part 1: Chemical contaminants. FødevareRapport 2005:01. http://gl.foedevarestyrelsen.dk/FDir/Publications/2005001/Rapport2.asp

GEUS (1998). Grundvandsovervågning 1998. Danmarks og Grønlands Geologiske Undersøgelse, Miljø- og Energiministeriet.

GEUS (2007). Grundvand. Status og udvikling 1989-2006. www.grundvandsovervaagning.dk

IARC (2004). Arsenic in drinking-water. In: IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 84 'Some Drinking-water Disinfectants and Contaminants, including Arsenic, Lyon, France, 39-267.

IRIS (2008). Arsenic, inorganic. In: Integrated Risk Information System. Database quest, last revised: Oral RfD 02/01/1993, carcinogenicity assessment 04/10/1998. US-EPA. http://www.epa.gov/ncea/iris/subst/0278.htm

JECFA (1983). 570. Arsenic. WHO Food Additive Series 18. http://www.inchem.org/documents/jecfa/jecmono/v18je17.htm

JECFA (1988). 658. Arsenic. WHO Food Additive Series 24. http://www.inchem.org/documents/jecfa/jecmono/v024je08.htm

JECFA (2010). Arsenic. In Summary and Conclusions from the Joint FAO/WHO Expert Committee on Food Additives Seventy-second meeting Rome, 16-25 February 2010, issued 16th March 2010. http://www.who.int/foodsafety/chem/summary72_rev.pdf

MM (2002). The Statutory Order from the Ministry of the Environment no. 439 of 3 June 2002, on the List of Chemical Substances.

MM (2001). Bekendtgørelse om vandkvalitet og tilsyn med vandforsyningsanlæg. Miljø- og Energiministeriets bekendtgørelse nr. 871 af 21. september 2001.

MST (1995). Toksikologiske kvalitetskriterier for jord og drikkevand. Projekt om jord og grundvand fra Miljøstyrelsen Nr. 12 1995, Miljøstyrelsen, Miljøministeriet.

MST (2002). B-værdivejledningen. Vejledning Nr. 2 2002, Miljøstyrelsen, Miljøministeriet.

MST (2004a). Diffus forurening og industri. Miljøstyrelsen, Miljøprojekt nr. 914, 2004.

MST (2004b). Diffus forurening og kulturlag. Miljøstyrelsen, Miljøprojekt nr. 912, 2004.

MST (2009). Personal communication from the Danish Environmental Protection Agency.

NST (2011). Personal communication from the Danish Nature Agency.

OEHHA (2004a). Public Health Goals for chemicals in drinking water: Arsenic. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, US. http://www.oehha.ca.gov/water/phg/pdf/asfinal.pdf

OEHHA (2004b). Public Health Goal for Arsenic. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, US. Fact Sheet. http://www.oehha.ca.gov/public_info/facts/pdf/Arsenicfinalphgfacts.pdf

OEHHA (2008). Final Statement of Reasons. Arsenic Primary Maximum Contaminant Level (MCL) Revision Title 22, California Code of Regulation. DPH-04-017, August 7, 2008. http://www.cdph.ca.gov/certlic/drinkingwater/Documents/Arsenic/DPH-17-04-ArsenicMCL-FSOR.pdf

OJ (1998). Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. Official Journal of the European Communities, 5.12.98, L 330/54. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:330:0032:0054:EN:PDF

SCHER (2010). SCHER (Scientific Committee on Health and Environmental Risks) scientific opinion on request for derogations on the Drinking Water Directive (Directive 98/83/EC), 16 April 2010. http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_120.pdf

Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Guha N, Freeman C, Galichet L, Cogliano V (2009). A review of human carcinogens - Part C: metals, arsenic, dusts, and fibres, on behalf of the WHO International Agency for Research on Cancer Monograph Working Group. International Agency for Research on Cancer, Lyon, France. Lancet **10**, 453-454.

US-EPA (2001).
http://water.epa.gov/lawsregs/rulesregs/sdwa/arsenic/regulations.cfm

US-EPA (2011).
http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=219111

WHO (1996). Arsenic. In: Guidelines for drinking-water quality, second edition, volume 2 Health criteria and other supporting information. World Health Organization, Geneva, 156-167.

WHO (2001). Arsenic and Arsenic Compounds (Second Edition). Environmental Health Criteria 224. World Health Organisation, International Programme on Chemical Safety, Geneva.

WHO (2003). Arsenic in Drinking-water. Background document for development of WHO *Guidelines for Drinking-water Quality*. World Health Organization, Geneva, WHO/SDE/WSH/03.04/75.

Arsenic, inorganic and soluble salts

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to the inorganic and soluble salts of arsenic. This resulted in 2011 in the present report which includes estimation of a quality criterion in drinking water for the mentioned substances.

Danish Ministry of the Environment
Environmental Protection Agency

Strandgade 29
1401 Copenhagen K, Denmark
Tel.: (+45) 72 54 40 00

www.mst.dk