

Arsenic and inorganic arsenic compounds

(with the exception of arsenic hydride and its salts)

BLW	50 µg arsenic and methylated metabolites/ l urine ¹ Sampling time: end of exposure or end of shift after several previous shifts
Date of evaluation	2002

Substance	CAS No.	Formula	Molecular weight	Melting point (°C)
arsenic	7440-38-2	As	74.92	817
arsenic trioxide	1327-53-3	As ₂ O ₃	197.82	193
arsenous acids	36465-76-6 13464-58-9	HAsO ₂ and H ₃ AsO ₃	125.94	not stated
and their salts, e.g.²				
sodium arsenite	7784-46-5	Na AsO ₂	191.89	not stated
arsenic pentoxide	1303-28-2	As ₂ O ₅	229.82	315
arsenic acid	7778-39-4	H ₃ AsO ₄	141.94	35
and its salts, e.g.				
lead arsenate	7778-39-4	Pb ₃ (AsO ₄) ₂	899.43	382
calcium arsenate	7778-44-1	Ca ₃ (AsO ₄) ₂	398.07	1

MAK [last established: 1971, 2002] Carcinogen category 1

(See also the documentation for carcinogenic substances for arsenic trioxide in Vol. 2)

Arsenic, arsenic trioxide and pentoxide, arsenous acids, arsenic acid and their salts (arsenites and arsenates) are carcinogenic substances (Carcinogen category 1) and do not, therefore, have MAK and BAT values (Greim 2002). The former TRK value (technical exposure limit) for arsenic and its inorganic compounds was 0.10 mg arsenic/m³ (measured as the inhalable fraction of the aerosol; calculated as arsenic). This arsenic concentration in air correlated with an arsenic concentration in urine of 130 µg/l at the end of exposure or the end of the shift after several previous shifts (see the EKA documentation for arsenic trioxide in Volume 2 of this series; Greim and Lehnert 1995). The inorganic arsenic and methylated metabolites are analysed together.

¹ volatile arsenic compounds determined by means of direct hydrogenation with hydride-AAS

² with the exception of gallium arsenide

In addition to their carcinogenic effects in man, arsenic and the above-named arsenic compounds have toxic effects on the skin, the nervous system and the vascular system. Even with internal exposure values to arsenic below those corresponding to external exposure to arsenic trioxide at the level of the TRK value (EKA_{TRK}), such toxic effects have been described, so that with exposure at the level of the EKA_{TRK} value protection against these effects is not guaranteed (Wichmann and Lehnert 1987).

1 Metabolism and Kinetics

1.1 Absorption and distribution

Man is exposed to different forms of organic and inorganic arsenic in foodstuffs, water and other matrices. Studies of the kinetics and metabolism of arsenic and its compounds are, therefore, complex. Inhalation exposure to inorganic arsenic occurs mainly at the workplace. In air, arsenic and its inorganic compounds are particle-bound and respiratory absorption therefore takes place in a two-phase process. After deposition of the particles in the respiratory tract and lungs, the arsenic is desorbed from the deposited particles. The extent to which the particles are deposited and the resulting exposure to arsenic therefore also depend on the size of the particles. Desorption of the arsenic compounds from the particles, however, depends on their solubility in water. For the reasons named, pulmonary retention cannot be estimated or quantified with sufficient certainty.

All water-soluble inorganic arsenic compounds are absorbed after ingestion to a considerable extent (up to 95 %) in the gastrointestinal tract (Marquardt 1997). The bioavailability depends, however, among other things also on the matrix of the foodstuff. Dermal absorption can be regarded as low compared to absorption after inhalation and gastrointestinal absorption (Wester *et al.* 1993).

Inhaled and ingested inorganic arsenic compounds first of all enter the blood. With a half-time of two hours, inorganic arsenic is rapidly eliminated from the blood. The arsenic compounds are distributed, as investigations with radioactively labelled arsenic compounds showed, in all the organs investigated. In addition to renal elimination, biliary excretion takes place. Experiments showed that elimination occurs in three phases in man. About 66 % of the administered doses is renally eliminated with a half-time of 2.1 days, around 30 % with a half-time of 9.4 days and the rest (4 %) with a half-time of 38.4 days (Marquardt 1997).

1.2 Metabolism

The metabolism of arsenic in man and in many species of animal takes place in two steps; first of all arsenic(V) is usually reduced to arsenic(III), which is then methylated to form monomethylated and dimethylated arsenic compounds. A detailed overview of

the metabolism of arsenic compounds can be found in the IPCS programme (WHO 2001) and in the EKA documentation for arsenic trioxide in Volume 2 of this series (Greim and Lehnert 1995).

2 Critical Toxicity

A detailed description of the symptoms of acute and chronic intoxication with arsenic can be found in the current WHO monograph on arsenic and arsenic compounds (WHO 2001).

2.1 Acute toxicity

The symptoms of intoxication after short-term and long-term absorption of inorganic arsenic compounds are similar and depend on the dose and bioavailability of the substance. The trivalent arsenic compounds are three to four times more toxic than the corresponding pentavalent compounds. The oral LD₅₀ values for inorganic arsenic compounds, depending on the arsenic species and the experimental animal, are in the range from 7 to 100 mg/kg body weight (Marquardt 1997).

The clinical symptoms after the ingestion of arsenic compounds occur within 30 to 60 minutes. Described are cardiovascular collapse, CNS depression and severe gastrointestinal symptoms. Death takes place within a few hours. With less dramatic cases of intoxication the main symptoms are gastrointestinal complaints including a metallic taste, a dry mouth, burning lips, dysphagia, vomiting attacks and occasional haematemesis.

2.2 Chronic toxicity

The carcinogenic effects of inorganic arsenic compounds have been demonstrated in epidemiological studies in man. In addition to tumours of the bronchi and the lungs, in particular the skin tumours (basaliomas situated on the trunk) are pathognomonic.

In addition to the carcinogenic effects, inorganic arsenic compounds cause damage in particular to the cardiovascular system and the nervous system. Long-term exposure to inorganic arsenic compounds is associated with cardiovascular diseases and cerebrovascular impairment. In particular the impairment of the peripheral vascular muscle-coat, even as far as gangrene of the affected extremities, has been consistently observed (WHO 2001). The neurotoxic effects can affect both the peripheral nervous system (Feldman *et al.* 1979, WHO 2001) and the central nervous system (WHO 2001).

Arsenic and its compounds are sensitizing to the skin only in exceptional cases and the described association between exposure to arsenic and diabetes mellitus needs further clarification (Rahman *et al.* 1995).

3 Exposure and Effects

Peripheral vascular diseases were described in persons who consumed spring water with a high arsenic concentration. Symptoms such as acrocyanosis and Raynaud's phenomenon were described after cumulative absorption of 8 g arsenic (Borgono *et al.* 1977). After cumulative absorption of 20 g arsenic, gangrene of the feet developed (Pershagen and Vahter 1979).

In occupationally exposed copper smelters, vasospastic changes in the arteries of the fingers were reported (Lagerkvist *et al.* 1986, 1988). The workers were mainly exposed to arsenic trioxide. The exposure was determined by analysing the inorganic arsenic and its metabolites in urine. The mean arsenic concentration in the urine of the exposed workers was 71 µg/l (range 10–340 µg/l), that of the asymptomatic controls 7 µg/l (range 5–20 µg/l). There were statistically significant differences between the exposed persons and the controls in the systolic blood pressure of the finger after cooling and the anamnesis of Raynaud's syndrome. It cannot be excluded, however, that in the past the exposure of the workers was much higher than at the time of the investigation. In the same group exposed to arsenic, the peripheral nervous system was investigated by means of electromyography and determination of the sensory nerve conduction velocity in the arms and legs. The exposed workers were found to have a slightly reduced nerve conduction velocity, which was interpreted as a subclinical sign of neuropathy (Blom *et al.* 1985). In another study, an increased incidence of clinically manifest and subclinical neuropathy in copper smelters was reported when the arsenic concentration in urine reached 250 µg/l (Feldman *et al.* 1979). One publication describes peripheral neuropathy in 51 persons with arsenic concentrations in urine above 100 µg/l (Heyman *et al.* 1956). Engel *et al.* (1994) give an overview of the vascular effects after long-term exposure to arsenic in their review based on 177 publications.

In studies of the nephrotoxic (Foà *et al.* 1987) and hepatotoxic effects (Kodama *et al.* 1976), statistically significant changes were found in exposed workers who excreted mean concentrations of arsenic in the urine of 102 µg/l and 82 µg/l, respectively.

To conclude, there are sufficient data from occupational-medical studies (see Table 1) which show adverse effects can occur at relatively low arsenic concentrations in urine, i.e. even below the former EKA_{TRK} of 130 µg/l.

Table 1. Relationship between adverse effects on health and the arsenic concentrations in occupationally exposed persons (modified from ACGIH (2001))

Observed effects	Arsenic in urine (µg/l) median (range)	Author
vasospastic tendency	71 (10–340)	Lagerkvist <i>et al.</i> 1986
peripheral neuropathy	71 (10–340)	Blom <i>et al.</i> 1985
peripheral neuropathy	< 250	Feldman <i>et al.</i> 1979
peripheral neuropathy	> 100	Heyman <i>et al.</i> 1956
impaired kidney function	103	Foà <i>et al.</i> 1987
increase in liver enzymes	82 ± 49 (SD)	Kodama <i>et al.</i> 1976

4 Selection of the Indicators

After exposure to inorganic arsenic there is a significant and specific increase in the arsenic species monomethylarsenic acid, dimethylarsinic acid and inorganic arsenic excreted in urine. The determination of these three arsenic species in urine is therefore the preferred method for the biological monitoring of workers exposed to inorganic arsenic. The determination of these arsenic species is not influenced by organic arsenic compounds, such as arsenobetaine and arsenocholine, taken up with food. Determination of the total amount of arsenic excreted in urine is not suitable for monitoring investigations because organic arsenic compounds of maritime origin are also determined (see the EKA documentation for arsenic trioxide in Volume 2 of this series; Greim and Lehnert 1995).

Inorganic arsenic and its metabolites are rapidly excreted after the beginning of exposure. The arsenic concentration in urine increases slowly and remains at a relatively constant level during the first three days of exposure. During the working day and from the end of work to the beginning of the next shift there are no notable changes in the concentration. The elimination kinetics show that during the working week there is significant accumulation of arsenic and its metabolites. Sampling should therefore take place at the end of the working week (see Section 1.1).

The determination of arsenic in blood and the arsenic concentrations in hair and finger nail samples have not acquired any importance in the biomonitoring of occupationally exposed persons (see the EKA documentation for arsenic trioxide in Volume 2 of this series; Greim and Lehnert 1995).

5 Methods

Inorganic and methylated organic arsenic compounds in urine are transformed for quantitative analysis into volatile hydrides and determined by atomic absorption spectroscopy. As a result of this method of direct hydrogenation of the urine sample only inorganic arsenic compounds and their metabolites monomethylarsenic acid and dimethylarsinic acid are transformed into volatile hydrides and quantified. A tested method can be found in "Analyses of Hazardous Substances in Biological Materials" (Angerer and Schaller 1991). If the urine sample is digested wet or dry the total arsenic content is determined. Therefore preparation of the urine samples should on no account be carried out. The following refers to the determination of inorganic arsenic and its methylated metabolites. In biological monitoring this arsenic fraction should be determined (Angerer and Schaller 1991).

6 Background Exposure

In persons not occupationally exposed, the diet is the main route of absorption for inorganic arsenic compounds. Food, with the exception of sea-food, contains less than 0.25 mg arsenic/kg; various kinds of fish between 1 and 10 mg/kg, and shell fish more than 100 mg/kg. In food of maritime origin the arsenic is in organic form, usually as arsenobetaine and arsenocholine. The daily uptake with food is estimated to be between 0.04 (without fish) and 0.19 mg arsenic (with fish). In comparison, in Germany, insignificant amounts of arsenic are taken up from the drinking water and air. With the hydride-AAS method suggested in Section 5 the aromatic arsenic compounds excreted unmetabolized in the urine are not determined. Under these analytical conditions the background exposure is below 25 µg/l urine. Recent investigations have shown, however, that also the level of excretion of the named arsenic fraction (inorganic arsenic, monomethylarsonic acid and dimethylarsinic acid) can be influenced by the consumption of large amounts of food of maritime origin. These foods can already contain the methylated substances, in particular dimethylarsinic acid (Apostoli *et al.* 1999). It is therefore recommended that in future only the inorganic arsenic fraction be determined. Separation of the arsenic species is, however, a time-consuming and complicated analytical procedure. Reference values for the various arsenic species in urine samples from the general population of northern Germany have been published (Heinrich-Ramm *et al.* 2001).

7 Evaluation of the BLW Value

The former TRK value for arsenic trioxide and pentoxide, arsenous acids, arsenic acid and their salts was 0.10 mg arsenic/m³ air. In 1994 an EKA correlation was established for arsenic trioxide, in which an arsenic concentration in the air of 0.10 mg/m³ corresponds to the excretion of 130 µg arsenic/l urine. The TRK value was not toxicologically grounded and observation of the value did not provide sufficient protection against the toxic effects named in Section 2.2.

For the prevention of (non-carcinogenic) toxic effects of arsenic, irrespective of the carcinogenic potency of arsenic, exposure should remain below 50 µg arsenic/l urine. Taking into account the literature cited, it is to be expected that arsenic-induced effects can develop at arsenic concentrations in urine in the range of 100 µg/l. Changes in the peripheral nerves of occupationally exposed persons were detected even at a mean arsenic concentration of 71 µg/l urine (Blom *et al.* 1985). The BLW value has therefore been set at

50 µg arsenic/l urine

This value is also compatible with the American BEI value (Biological Exposure Indices) (35 µg arsenic/l urine, sampling at the end of the working week), as this refers to the collective median and does not represent an individual ceiling value (ACGIH 2001).

8 Interpretation of Data

The toxicologically relevant arsenic concentration in urine is determined with the method described in “Analyses of Hazardous Substances in Biological Materials” (Angerer and Schaller 1991). The arsenic taken up with food of maritime origin is not determined. The use of the so-called hydride method is therefore imperative. The total amount of arsenic renally excreted must not be determined after preparation of the urine sample as the results can be greatly influenced by the food consumed. Fish and other sea-food can contain a high level of organic arsenic compounds. These compounds are rapidly absorbed by the gastrointestinal tract and can lead to the increased excretion of arsenic in urine. Arsenic concentrations in urine in the range of the BLW value can be reached and even exceeded (Mindt-Prüfert *et al.* 1999).

It should also be noted that also with the use of the hydride-AAS method, the excretion of inorganic arsenic and its methylated metabolites can be influenced by high fish consumption (Apostoli *et al.* 1999). Fish can also frequently contain methylated arsenic compounds (in particular dimethylarsinic acid). The total amount of arsenic in urine can, therefore, be increased.

If the BLW is exceeded, the individual should be specifically asked about his fish consumption over the last few days, and if necessary the arsenic concentration should be redetermined after a period without fish. After a single meal containing sea-food contaminated with organic arsenic compounds, the amount of arsenic excreted within 24 hours was 50 % to 70 % of the total amount of arsenic taken up (Marquardt 1997). Short-term control investigations can therefore be useful.

In some countries, such as Bangladesh, Argentina, Chile and India, considerable amounts of arsenic are taken up by the general population with the drinking water from contaminated wells. This causes amounts of arsenic to be excreted in urine which are above the BLW value (WHO 2001).

9 References

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