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Arsenic and inorganic arsenic compounds (with the exception of arsine) – Addendum: Re-evaluation of BLW and EKA

Assessment Values in Biological Material – Translation of the German version from 2023

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area re-evaluated the exposure equivalents for carcinogenic substances (EKA) as well as the biological guidance value (BLW) for arsenic [7440-38-2] and inorganic arsenic compounds with the exception of arsine. Recent findings on formation and renal excretion of the arsenic metabolite dimethylarsinic acid suggest substantial alimentary influence on this parameter, which has been used as biomarker besides other metabolites. In order to increase the diagnostic reliability, EKA were derived without the use of dimethylarsinic acid as marker for internal exposure, taking into account now the metabolites arsenic(III), arsenic(V) and monomethylarsonic acid. Furthermore, the range of the EKA was extended to concentrations below 1 µg/m^3. Analogous to the EKA derivation, the BLW was re-evaluated based on the renal excretion of the species arsenic(III), arsenic(V) and monomethylarsonic acid. To prevent peripheral neuropathy as the most critical systemic toxic effect besides carcinogenicity, an average concentration of 10 µg/l for the sum of arsenic(III), arsenic(V) and monomethylarsonic acid should not be exceeded in post shift urine samples.

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BLW (2022)

10 µg Σ As(III), As(V) and monomethylarsonic acid/l urine

EKA (2022)

The following correlations between external and internal exposure are obtained:

Air **Arsenic and inorganic arsenic compounds (with the exception of arsine)** **[µg As/m³][a)]**	Urine **Σ Arsenic(III), arsenic(V), monomethylarsonic acid** **[µg/l]**
0.5	2.0
0.8	2.5
1	3.0
5	8.0
8.3	11.0
10	13.0
50	36.0
100	57.0

[a)] determined in the I (inhalable) fraction

BAR (2015)

0.5 µg Arsenic(III)/l urine
0.5 µg Arsenic(V)/l urine
2 µg Monomethylarsonic acid/l urine
10 µg Dimethylarsinic acid/l urine

Sampling time: end of exposure or end of shift

MAK value	–
Peak limitation	–
Absorption through the skin (2014)	H
Carcinogenicity (1971)	Category 1
Prenatal toxicity	–
Germ cell mutagenicity (2002)	Category 3 A

Re-evaluation

In 1993, exposure equivalents for carcinogenic substances (EKA) were derived for arsenic trioxide (translated in Schaller 1995). In 2002, for arsenic and inorganic arsenic compounds, a biological guidance value (BLW) of 50 µg inorganic arsenic and methylated metabolites (volatile arsenic compounds determined by direct hydrogenation)/l urine was derived (translated in Drexler 2005) and in 2010 a biological reference value (BAR) of 15 µg inorganic arsenic and methylated metabolites (volatile arsenic compounds determined by direct hydrogenation)/l urine was set (translated in Ochsmann et al. 2019). In 2015 BARs for the arsenic species arsenic(III) (As^{3+}; 0.5 µg/l urine), arsenic(V) (As^{5+}; 0.5 µg/l urine), monomethylarsonic acid (2 µg/l urine) and dimethylarsinic acid (10 µg/l urine) were evaluated. At the same time, EKA based on the sum of the compounds mentioned were established (translated in Ochsmann et al. 2018).

Recent findings on the formation and renal excretion of the arsenic metabolite dimethylarsinic acid suggest substantial dietary effects on this parameter. The present addendum therefore examines whether the diagnostic validity of exposure monitoring after occupational arsenic exposure can be further increased without the use of the parameter dimethylarsinic acid. Furthermore, it is examined whether the derivation of a BLW can be based on the determination of the above-mentioned arsenic species and whether the EKA can be extended to concentrations below 1 µg/m^3 and thus into the range of the currently valid acceptance concentration of 0.8 µg/m^3.

Selection of the indicators

Precise, validated methods are available for determining the internal arsenic exposure, which make it possible to draw conclusions about the levels of individual arsenic species such as arsenic(III), arsenic(V), monomethylarsonic acid or dimethylarsinic acid in addition to the total arsenic content in urine (Begerow et al. 2001; Schramel et al. 2018). After exposure to inorganic arsenic at the workplace, a determination of those arsenic species in the urine is particularly recommended that allow a differentiation from arsenic compounds taken up with food (Ochsmann et al. 2018).

Analytical methods

For the determination of arsenic species in urine, two methods are available that have been evaluated by the working group "Analyses in Biological Materials". One method is based on the coupling of liquid chromatography, a post-column derivatisation to arsine and atomic absorption spectrometry (HPLC-AAS) (Begerow et al. 2001). It allows detection limits of 0.9 µg arsenic/l for arsenite (arsenic(III)), 2.0 µg arsenic/l for arsenate (arsenic(V)), 1.4 µg arsenic/l for monomethylarsonic acid and 2.3 µg arsenic/l for dimethylarsinic acid. Another method is based on the coupling of liquid chromatography and inductively coupled plasma mass spectrometry (HPLC-ICP-MS) (Schramel et al. 2018). This method allows the determination of analytes with the following detection limits: 0.03 µg arsenic/l for arsenite, 0.05 µg arsenic/l for arsenate, 0.04 µg arsenic/l for monomethylarsonic acid and 0.02 µg arsenic/l for dimethylarsinic acid. Furthermore, the method allows a determination of arsenobetaine with a detection limit of 0.03 µg arsenic/l. The latter method is thus comparable to the analytical methods described and used by Leese et al. (2014), Morton and Leese (2011) and Heitland and Köster (2008, 2009).

Formation and excretion of dimethylarsinic acid

The excretion of inorganic arsenic takes place predominantly via the kidneys in the form of various arsenic species. With the transition from the detection of hydride-forming arsenic compounds in urine to the targeted determination of defined arsenic species, the selectivity of exposure monitoring after exposure to inorganic arsenic has been increased. In this way, a co-recording of hydride-forming but toxicologically irrelevant organic arsenic compounds (e.g. arsenosugars) is avoided (Ochsmann et al. 2018). Among the four species considered, namely arsenic(III), arsenic(V), monomethylarsonic acid and dimethylarsinic acid, dimethylarsinic acid is excreted in the highest concentrations. At moderate levels of exposure, arsenic in human urine is present at 10–30% as inorganic species (arsenic(III) or (V)), at 10–20% as monomethylarsonic acid and at 60–80% as dimethylarsinic acid; the composition of which can vary depending, among others, on the individual methylation capacity (Agusa et al. 2011; EFSA 2009).

Studies on the excretion of dimethylarsinic acid showed a dependence of the parameter on dietary effects. In a comparative study of subjects with and without consumption of seafood, there was only a very slight effect of the diet on the excretion of inorganic arsenic and monomethylarsonic acid. In contrast, a strong increase in the concentration of dimethylarsinic acid in the urine was found, especially after the consumption of mussels (Buchet et al. 1996).

In a study with four test persons, Ma and Le (1998) demonstrated an increase in the concentration of dimethylarsinic acid in urine after the consumption of seaweed (two 10-g portions within 6 hours), which lasted for a period of about 60 hours. Since tests of the ingested algae for dimethylarsinic acid showed only low levels, the authors attributed their observations to a metabolic formation of dimethlyarsinic acid from arsenosugars contained in the algae. Evidence for a corresponding metabolisation was provided in studies by Francesconi et al. (2002) and Raml et al. (2005, 2009), who

detected dimethylarsinic acid as the main metabolite in urine samples of test persons after ingestion of synthetic arsenosugars. The later studies revealed a high interindividual variability of the metabolisation of arsenosugars and the excretion of dimethylarsinic acid (Raml et al. 2009).

Another study with sixteen test persons confirms the significant influence of the diet with marine food products on the excretion of dimethylarsinic acid. Within a 6-day period with daily intake of marine food (67.5% algae products, 32.5% fish and seafood), arsenic excretion (hydride-forming species) in morning urine samples increased 20- to 25-fold compared to control samples before the consumption phase. The initial values were reached again 5 days after the last consumption. With at most minor changes in the concentration of the arsenic species arsenic(III), arsenic(V) and monomethylarsonic acid over time, the massive increase in arsenic concentrations was predominantly due to an increase in the excretion of dimethylarsinic acid (Choi et al. 2010).

Arsenosugars that can be metabolised to dimethylarsinic acid are often found in marine algae, but they can also be present in molluscs and crustaceans that feed predominantly on algae and phytoplankton (Taylor et al. 2017), for example in freshwater and saltwater mussels and oysters (Ma and Le 1998).

The arsenosugars found in marine algae are predominantly ribose derivatives that carry a dimethylarsinoyl group on the C5 atom of the ribose residue, while the C1 atom can have various substituents (Figure 1).

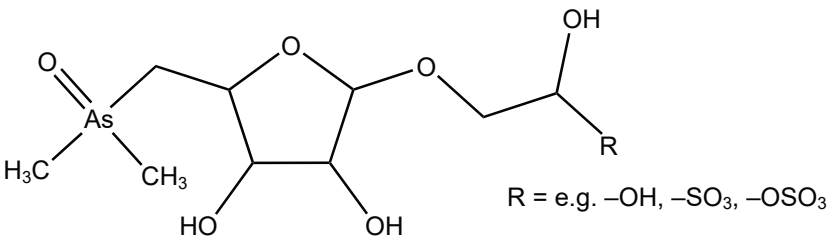

Fig. 1 Structure of arsenosugars found in marine algae (according to Taylor et al. 2017)

In addition to dimethylarsinic acid, the oxo- and thio-analogues of dimethylarsenoethanol and dimethylarsenoacetate as well as another unknown metabolite were detected in the urine after the ingestion of arsenosugars. These compounds are thought to be intermediates in the metabolic conversion of arsenosugars to dimethylarsinic acid (Raml et al. 2005; Taylor et al. 2017). The metabolic formation of dimethylarsinic acid from arsenosugars thus takes place from already dimethylated precursors and does not require endogenous methylation in which monomethylarsonic acid could occur as an intermediate. The latter explains why the parameter monomethylarsonic acid in urine, unlike dimethylarsinic acid, is hardly affected by the consumption of seaweed.

According to the results of Hata et al. (2016), a close correlation of the sum parameters Σ arsenic(III), arsenic(V), monomethylarsonic acid and Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid in urine can be assumed if only an intake of inorganic arsenic takes place ($r = 0.962$; $p < 0.0001$; 330 subjects from Bangladesh with arsenic intake from drinking water). However, consumption of marine food resulted in a weaker association between the two sum parameters ($r = 0.698$; $p < 0.0001$; 172 subjects from Japan). The observed effect was attributed to the additional ingestion of arsenosugars in marine algae and their metabolisation to dimethylarsinic acid. This leads to an increased excretion of dimethylarsinic acid, but not of the other three arsenic species. Due to the fact that dimethylarsinic acid excretion can be influenced by food, Hata et al. (2016) recommend using the arsenic species arsenic(III), arsenic(V) and monomethylarsonic acid for the investigation of exposures to inorganic arsenic. A corresponding approach can be found, for example, in recent studies investigating the intake of inorganic arsenic in the general population of Japan (Oguri et al. 2017; Yoshinaga and Narukawa 2020). Another study of arsenic exposure in 149 workers at a copper smelter found weak but significant associations with external exposure for the parameters Σ arsenic(III), arsenic(V) in urine ($r = 0.300$; $p < 0.05$) and Σ arsenic(III), arsenic(V), monomethylarsonic acid in urine ($r = 0.286$; $p < 0.05$), but not for the parameter Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid in urine. As a cause for the

lack of association when dimethylarsinic acid was additionally considered, the authors suspected an intake of arsenic through marine food in some of the subjects (Janasik et al. 2015).

Re-evaluation of the EKA

The derivation of the EKA in 2016 was based on a study by Apostoli et al. (1999), in which correlations between arsenic exposure in the air and the excretion of the arsenic species arsenic(III), arsenic(V), monomethylarsonic acid and dimethylarsinic acid in urine were investigated in workers exposed to arsenic trioxide in the glass industry. In the study by Apostoli et al. (1999), in addition to a regression equation for the association between arsenic in air and the Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid in urine, regression equations are given for the associations between arsenic in air and the concentrations of the individual arsenic species as well as the sum of inorganic arsenic (Σ arsenic(III), arsenic(V)) in urine. This information indirectly allows the derivation of a correlation between the arsenic concentration in air and the sum concentration of the parameters arsenic(III), arsenic(V) and monomethylarsonic acid (Σ arsenic(III), arsenic(V), monomethylarsonic acid) in urine. As Table 1 shows, an "indirect" calculation of the concentrations for the parameter Σ (arsenic(III), arsenic(V)), monomethylarsonic acid, dimethylarsinic acid via separate regression equations and their subsequent summation (Table 1, column 3) leads to similar results as the calculation via the previously used "direct" regression equation for the sum of the measured individual concentrations (Table 1, column 2). An analogous calculation of the sum of inorganic arsenic and monomethylarsonic acid without dimethylarsinic acid via separate regressions for the individual parameters Σ (arsenic(III), arsenic(V)) and monomethylarsonic acid therefore appears justifiable (Table 1, column 4). The parameters Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid (Table 1, column 2) and Σ (arsenic(III), arsenic(V), monomethylarsonic acid (Table 1, column 4) show – as expected for exposure to inorganic arsenic (see also Hata et al. 2016) – a close linear relationship ($\mathbf{y = -5.876 + 0.481x}$; $r = 0.993$; $p < 0.001$).

To take into account the concentrations for acceptance risk (0.8 µg As/m^3, risk 4 : 10 000) and tolerance risk (8.3 µg As/m^3, risk 4 : 1000) mentioned in the exposure-risk relationship (ERB) of the Committee for Hazardous Substances at the Federal Ministry of Labour and Social Affairs (AGS 2015), corresponding equivalents in biological material were also calculated and the relationships were considered down to a lower concentration of 0.5 µg As/m^3 air.

Tab. 1 "Indirect" calculation of the concentrations Σ arsenic(III), arsenic(V), monomethylarsonic acid and Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid in urine at given levels of exposure to arsenic in air using the regression equations for the individual parameters according to Apostoli et al. (1999) and comparison of the results for Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid with the values previously used for EKA derivation, which were obtained by means of "direct" regression

Air	Urine		
Arsenic and inorganic arsenic compounds (with the exception of arsine)	**Σ Arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid** from direct regression: log y [µg/l] = 1.186 + 0.455 log x [µg/m³]	**Σ (Arsenic(III), arsenic(V)), monomethylarsonic acid, dimethylarsinic acid** as the sum of the concentrations of the individual parameters: log y [µg/l][a] = 0.090 + 0.635 log x [µg/m³] log y [µg/l][b] = 0.221 + 0.655 log x [µg/m³] log y [µg/l][c] = 1.067 + 0.364 log x [µg/m³]	**Σ (Arsenic(III), arsenic(V)), monomethylarsonic acid** as the sum of the concentrations of the individual parameters: log y [µg/l][a] = 0.090 + 0.635 log x [µg/m³] log y [µg/l][b] = 0.221 + 0.655 log x [µg/m³]
[µg As/m³]	**[µg/l]**	**[µg/l]**	**[µg/l]**
100[d]	125[d]	119	56.9
50[d]	91[d]	85	36.3
10[d]	44[d]	40	12.8
8.3	40	37	11.4
5[d]	34[d]	30	8.2
1[d]	15[d]	15	2.9
0.8	14	13	2.5
0.5	11	11	1.8

[a] arsenic(III) + arsenic(V)
[b] monomethylarsonic acid
[c] dimethylarsinic acid
[d] values used to derive the previous EKA

When comparing the correlations of Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid and Σ arsenic(III), arsenic(V), monomethylarsonic acid in urine shown in Table 1 on the basis of the data of Hata et al. (2016), the agreements with the values calculated by regression according to Apostoli et al. (1999) are in part very good, especially for the concentration range up to 10 µg As/m³ air. The correlation between arsenic exposure in the air and the excretion of inorganic arsenic and monomethylarsonic acid is also supported by calculations by Janasik et al. (2015), according to which, for the parameters mentioned, an excretion of 12.7 µg/l urine can be expected for a concentration of 10 µg As/m³ air for employees of a copper smelter. In studies by Sińczuk-Walczak et al. (2014) examining 21 employees of a Polish copper smelter exposed to a mean air concentration of 25.2 µg/m³ (range 0.7–92.3 µg/m³), mean internal exposure levels of 56.2 µg/l urine (range 15.2–108.6 µg/l) for Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid and 22.4 µg/l urine (range 3.4–51.1 µg/l) for Σ arsenic(III), arsenic(V), monomethylarsonic acid were obtained . Calculating the internal exposures based on the air concentrations with the help of the correlations shown in Table 1 results in equivalents of 65.1 µg/l (Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid) and 23.2 µg/l (Σ arsenic(III), arsenic(V), monomethylarsonic acid), respectively, which show very good agreement with the determined values. Based on the available data, the following EKA are derived for arsenic and inorganic arsenic compounds with the exception of arsine:

Air Arsenic and inorganic arsenic compounds (with the exception of arsine) [µg As/m³][a)]	Urine Σ Arsenic(III), arsenic(V) and monomethylarsonic acid [µg/l]
0.5	2.0
0.8	2.5
1	3.0
5	8.0
8.3	11.0
10	13.0
50	36.0
100	57.0

[a)] determined in the I (inhalable) fraction

Sampling time is at the end of exposure or at the end of shift.

Re-evaluation of the biological guidance value (BLW)

The biological guidance value of 50 µg arsenic/l urine derived in 2002 refers to the excretion of arsenic compounds that can be converted into volatile arsenic compounds by direct hydrogenation. The latter can be determined analytically as sum parameter. In view of the facts that, unlike then, individual species are analysed now and the BLW was derived as a ceiling value at that time, it has become necessary to examine an adjustment of the value.

The basis for deriving the value was a study by Blom et al. (1985), in which reduced peripheral nerve conduction velocities were detected in a collective of 47 workers of a Swedish copper smelter who had been exposed to arsenic trioxide for many years. The deviations compared to an age-matched, non-exposed control group were interpreted in the sense of a subclinical neuropathy. The external exposure of the workers was about 50 µg/m³ in the last 7 years prior to the study, before that the exposures ranged up to 500 µg/m³. The mean internal exposure (volatile arsenic compounds determined by direct hydrogenation) for the exposed workers was 71 µg/l urine (range: 10–340 µg/l), while a mean of 7 µg/l (range: 5–20 µg/l) was determined in the urine of the control group (Blom et al. 1985; Drexler 2005).

Due to the demonstrated subclinical changes, the described external and internal exposures of the exposed workers are to be regarded as LOAEL (lowest observed adverse effect level). If the factor 3 (ECETOC 2003) is taken into consideration for the extrapolation from a LOAEL to a NOAEL (no observed adverse effect level), a corresponding NOAEL of 24 µg/l is calculated for the Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid based on the mean internal exposure of 71 µg/l urine. A direct conversion of the value of 71 µg/l for the parameter Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid into a concentration for the parameter Σ arsenic(III), arsenic(V), monomethylarsonic acid using the above regression equation ($y = -5.876 + 0.481x$; $r = 0.993$; $p < 0.001$) derived from the data of Apostoli et al. (1999), yields a value of 28 µg/l and thus a NOAEL of 9 µg/l.

In a study with 21 workers of a Polish copper smelter (mean internal exposure of 56.2 µg/l urine (range: 15.2–108.6 µg/l) for Σ arsenic(III), arsenic(V), monomethylarsonic acid, dimethylarsinic acid and of 22.4 µg/l urine (range: 3.4–51.1 µg/l) for Σ arsenic(III), arsenic(V), monomethylarsonic acid), neurological effects were detected that correlated with the level of external or internal exposure (Sińczuk-Walczak et al. 2014). The authors concluded that exceeding the BEI (biological exposure index) of 35 µg arsenic/l urine is associated with the occurrence of symptoms of peripheral polyneuropathy. However, a described, in some cases considerable, co-exposure to lead (mean blood level 254 µg/l, range 71–468 µg/l) limits the significance of these findings for a BLW derivation.

Taking into consideration the data presented, the occurrence of peripheral polyneuropathies apart from carcinogenicity is still to be regarded as the critical systemic toxic effect for the derivation of a BLW. For the prevention of corresponding neurological damage, the BLW is set at

10 µg Σ arsenic(III), arsenic(V) and monomethylarsonic acid/l urine.

Sampling time is at the end of exposure or at the end of shift.

Interpretation of the results

When interpreting data on internal arsenic exposure, attention must be paid to the dietary habits of the persons examined. This includes, in particular, previous fish consumption or consumption of seafood, which can temporarily lead to a strong increase in the intake of organic arsenic compounds. The influence of the dietary intake of organoarsenic compounds on the analysis results should be minimised by examining urine samples by means of species analysis and reference to the parameters arsenic(III), arsenic(V) and monomethylarsonic acid. Nevertheless, it seems advisable to record the dietary habits before taking the samples. Furthermore, regional influences should be taken into account, since natural contamination of drinking water with arsenic varies greatly from region to region and can therefore affect the results of the analysis. In addition, age, gender, smoking and alcohol consumption have also been identified as possible factors influencing arsenic concentrations in biological materials (see for example Heinrich-Ramm et al. 2001; Leese et al. 2014).

All assessment values in biological material refer to normally concentrated urine, in which the creatinine content should be between 0.3 and 3.0 g/l urine. As a rule, for urine samples outside the limits mentioned, it is recommended to repeat the measurement in the normally hydrated test person (translated in Bader et al. 2016).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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