HBM4EU science and policy for a healthy future

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HBM4EU

POLICY BRIEF

JULY 2022

European Human Biomonitoring Initiative

Arsenic

This policy brief summarizes the adverse human health effects of arsenic, its main exposure pathways for humans, and how human biomonitoring (HBM) of arsenic could be of value in the development of EU policies.

Arsenic occurs naturally in the earth's crust and is considered a significant environmental toxicant. Anthropogenic sources of arsenic are emitted into the air, water, and soil where the pathway to environmental species, ecosystems and humans is more direct. Based on the combination of natural occurrence and anthropogenic activities, the contamination of soil and drinking water by arsenic is globally threatening human health. Arsenic can occur in two forms, organic or inorganic. This policy brief refers to its inorganic form (iAs) as it poses a greater risk for human health due to its higher toxicity and is the predominant environmental contaminant.

KEY MESSAGES

- **HBM4EU Aligned Studies[1] (2014-2021) have generated baseline levels of internal exposure to inorganic arsenic in teenagers in 6 sampling sites (BE, DE, ES, SE, SL and FR).**
- **HBM data were compared with iAs exposure estimates from dietary intake and matched well, indicating that main iAs intake of the general population is through dietary exposure.**
- **HBM data were compared with already available health related guidance values for cancer and for non-cancer effects. Between 15.6 and 52.0% of study participants exceeded the Biomonitoring equivalent set as a guidance value to prevent adverse effects (hyperpigmentation and vascular complications).**
- **The daily intake dose of iAs that was estimated based on average HBM levels from HBM studies and kinetic modelling (0.16 µg kg-1 bw/day) corresponded with a lifetime excess lung cancer risk of 2.7 x 10^{-4}.**

BACKGROUND: HBM4EU

The European Human Biomonitoring Initiative, HBM4EU, running from 2017 to June 2022, is a joint effort of 28 countries, the European Environment Agency and the European Commission, and co-funded under Horizon 2020. The main aim of the initiative is to coordinate and advance human biomonitoring in Europe. HBM4EU has provided a wealth of improved evidence of the actual exposure of citizens to chemicals and their possible health effects. Human biomonitoring allows us to measure our exposure to chemicals by measuring either the substances themselves, their metabolites or markers of subsequent health effects in body fluids or tissues. Information on human exposure can be linked to data on sources and epidemiological surveys to inform research, prevention, and policy with the objective of addressing knowledge gaps and promoting innovative approaches. If you would like to read more about the project itself, please visit the HBM4EU website.

1 The HBM4EU Aligned Studies are a survey aimed at collecting HBM samples and data as harmonised as possible from (national) studies to derive current internal exposure data representative for the European population/citizens across a geographic spread.

HBM4EU RESULTS

To further support current and future HBM studies, HBM4EU has produced a variety of publicly available groundwork materials for a harmonised approach to study planning and conduct in Europe, available in the HBM4EU online library.

The main results for arsenic include the following:

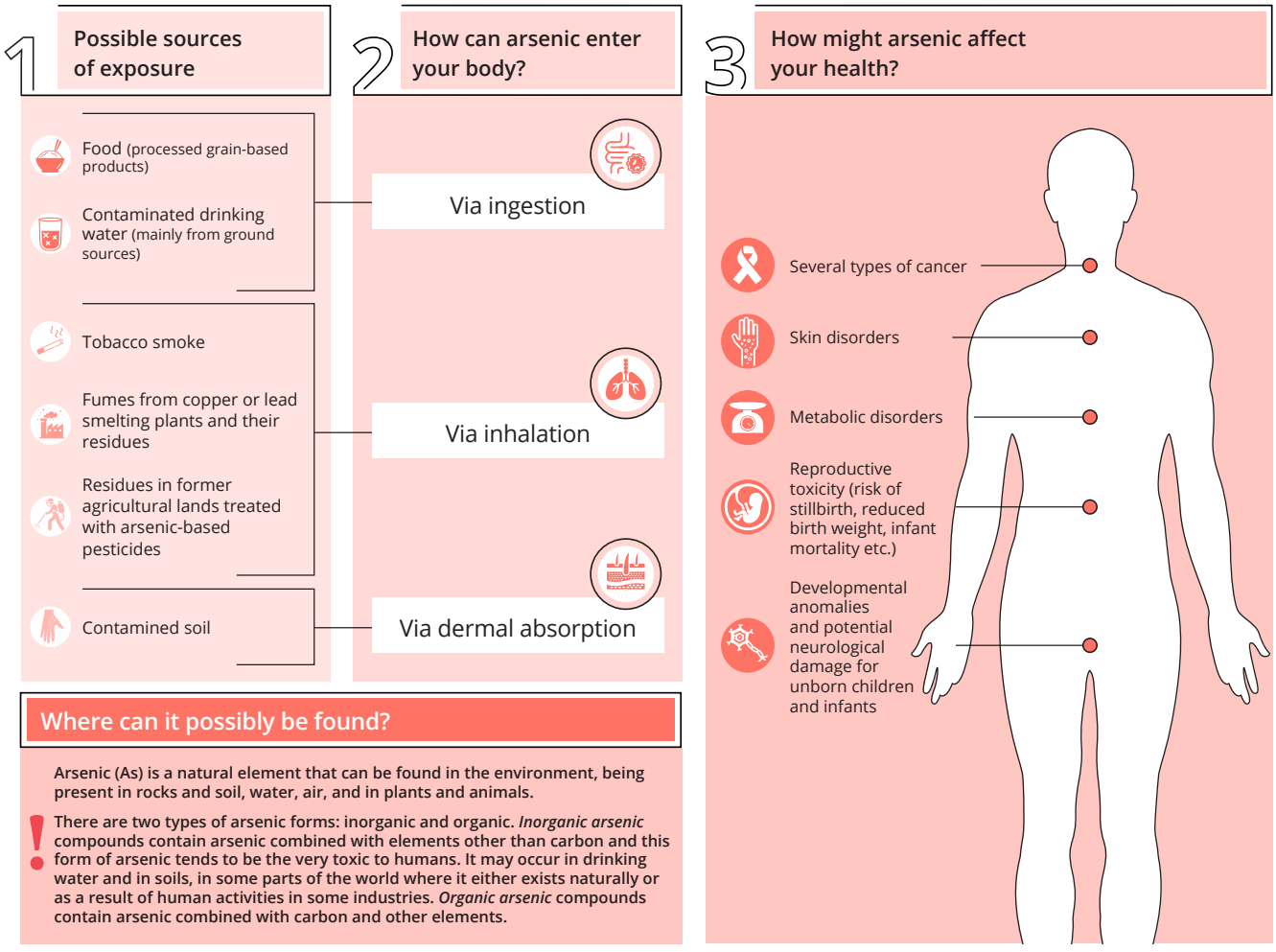
- An overview of available HBM data on arsenic from European studies (Tables 1 in scoping document).
- Reliable data collection available in IPCHEM, the Information Platform for Chemical Monitoring as well as in the European HBM Dashboard.
- A list of approved laboratories to carry out arsenic analyses was implemented through a quality assurance/quality control Programme as part of a HBM European Platform. These laboratories are equally qualified for exposure biomarker analysis.
- A journal publication on the association between asthma and environmental chemicals (including arsenic).
- A comparison of newly obtained HBM data from teenagers with health-based biomonitoring guidance values

EXPOSURE & HEALTH EFFECTS

Susceptibility to the toxic effects of arsenic varies considerably between individuals and populations depending on variations in metabolism related to factors such as age, sex, life stage (e.g. pregnancy, lactation), genetic diversity, and nutritional status (EFSA, 2014). This complicates the assessment of health impacts caused by arsenic and highlights the importance of HBM data.

An overview of main sources of exposure (environmental, occupational, consumer), exposure pathways (oral, inhalation, dermal) and health effects are provided in Figure 1.

Figure 1. Overview of exposure sources, pathways and health effects of arsenic



INPUT TO POLICY PROCESSES AND RELEVANT POLICY MEASURES

HBM4EU results have contributed to consultations for the Chemicals' Strategy for Sustainability and the Zero-Pollution Action Plan. These are available in the HBM4EU Science to Policy section.

Existing EU policies cover regulations on chemicals, consumer products, the environment and occupational exposure.

Arsenic is registered under REACH (Regulation (EC) No 1907/2006) with specific uses further controlled under Annex XVII (restriction). It is subject to EU harmonised classification and labelling under CLP (Regulation on the classification, labelling and packaging of substances and mixtures), Regulation (EC) No 1272/2008.

The Drinking Water Directive (98/83/EC) limits the concentration of arsenic in water for public consumption to 10 µg/L. And the Directive (EU) 2016/2284 on the reduction of national emissions of certain atmospheric pollutants requires Member States to report arsenic pollution annually.

Maximum levels for arsenic in certain foods have been established by Regulation (EC) No 2015/1006 (e.g. rice waffles 0.30 µg/kg).

Directive (EU) 2019/983 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work introduces an occupational limit value for arsenic inhalation. The limit value (0.01 mg/m3) for arsenic applies from 11 July 2023 for the copper smelting sector.

POLICY QUESTIONS

The answers to the policy questions below are summarised. For more details, please see the Substance Reports available on the substance specific page of the HBM4EU website.

1 What is the current exposure of the EU population to arsenic?

When identifying exposure levels and sources as well as groups at risk, HBM4EU developed valuable questionnaires. These can be used to set up new studies and allow for the harmonized collection of data on a participants' individual characteristics and their potential exposure pathways from different sources (sociodemographic characteristics, residential environment/ home exposures, dietary habits, lifestyle, occupational exposure and health status). For arsenic, questionnaires for adolescents and adults are available.

Speciated arsenic in urine (iAs III, iAs V, MMA, and DMA) are the preferred biomarker(s) for exposures to inorganic arsenic. The sum of As(III), As(V), MMA and DMA provide a measure of exposure to inorganic As, however DMA may also originate from less toxic organic As species.

New HBM data collected in HBM4EU Aligned Studies show that P50 and P95 sum of DMA + MMA + As(III) + As(V) concentrations in teenagers are in the range of 2.27-5.52 µg/g crt and 6.65-15.93 µg/g crt respectively. The share of individuals with exposure levels exceeding the BE-value of 6.4 µg/L range from 15.63-52.00%. The extent of exceedance ranges from 1.55-3.36 in teenagers.

P50 and P95 DMA concentrations are in the range of 1.44-3.59 µg/g crt and 5.01-12.57 µg/g crt, respectively.

P50 and P95 MMA concentrations are in the range of 0.36-1.02 µg/g crt and 0.84-2.57 µg/g crt, respectively. P50 and P95 As(III) concentrations are in the range of 0.11-0.31 µg/g crt and 0.46-0.98 µg/g crt, respectively. P50 and P95 As(V) concentrations are in the range of 0.14-0.24 µg/g crt (3 studies P50< detection level: 0.1 µg/L) and 0.22-1.01 µg/g crt (1 study P95 < detection level: 0.1µg/L), respectively.

P50 and P95 arsenobetaine concentrations are in the range of 0.39-8.28 µg/g crt and 17.88-128.02 µg/g crt, respectively. Arsenobetaine (Asb) is mainly derived from fish intake and is considered less toxic.

2 What biomonitoring and exposure (environmental and occupational) data on arsenic, relevant to the European population, are currently available?

In the HBM4EU Aligned Studies, arsenic has been assessed in six teenager studies consisting of 1445 teenagers between 12 and 18 years. Total As in urine is available in 596 teenagers; As III, As V, DMA, and MMA in 586 teenagers; and Asb in 505 teenagers.

Occupational exposure in Europe is limited to the hotspot and therefore recent data on the magnitude of workers' exposure to this element are lacking.

3 What is the geographic spread of the current exposure and how does it relate to different exposure sources (environmental/dietary)?

The main source of iAs is diet, especially rice and other cereals, juices, and seafood. Current exposure of the general EU population to arsenic from drinking water is low due to the limited presence of iAs in drinking water in most areas.

Average iAs exposure levels (daily doses) calculated based on food consumption data and iAs concentrations in food were in the range of 0.07 to 0.20 µg kg-1 bw/day for seven age-stratified population groups (from toddlers to very elderly) and P95 levels lay between 0.19 and 0.64 µg kg-1 bw/day.

iAs exposure estimates from dietary intake were compared with existing HBM data and matched well, indicating that the main iAs intake of the general population is dietary exposure.

The analyses in the HBM4EU Aligned Studies focused on the differences in exposures based on diet. The sum of As(III), As(V), MMA, and DMA was associated with (recent) seafood and/or rice consumption in European teenagers.

4 Which population groups are most at risk?

Concerning the studies compiled before HBM4EU, it could not be assessed which population groups are most at risk due to the diversity in study design, sampled matrices, analytical techniques, and sampling periods.

However, long-term exposure to arsenic can cause cancer and skin lesions. It has also been associated with cardiovascular disease and diabetes. In utero and early childhood, exposure has been linked to negative impacts on cognitive development and reduced birth weight, as well as premature deaths in young adults. This does not apply to low doses, but rather to long-term exposure to As in drinking water in the ranges of 50-100 mcg/l (WHO, 2018).

In the HBM4EU Aligned Studies, arsenic exposure was measured in teenagers. HBM data were compared with already available health-based guidance values for cancer and for non-cancer effects. Between 15.6 and 52.0% study participants exceeded the Biomonitoring Equivalent set as a guidance value to prevent adverse effects (hyperpigmentation and vascular complications). Sex and socio-economic status (SES) were no major exposure determinants in the aligned studies.

The daily intake dose of iAs (0.16 µg kg-1 bw/day including iAs, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA)) that was estimated based on average HBM levels from 28 HBM studies in different population groups in the EU, and kinetic modelling corresponded with a lifetime excess lung cancer risk of 2.7 x 10-4. The approach can be considered as conservative, overestimating the risk especially at low exposure levels.

Susceptible subgroups may also be identified based on the mode of action of arsenic (which has not been fully elucidated). For instance, endocrine disruption by arsenic may be mediated via hormone receptors or steroid levels, which may differ across life stages or physiologic conditions resulting in differences in susceptibility between individuals.

5 What factors (genetic polymorphisms) make people more susceptible or not to the risk of health effects due to arsenic exposure? What are the most sensitive biomarkers for identification of reliable arsenic exposure and potential adverse health-effect?

Many studies indicate the relationship between the genetic polymorphism of arsenic-metabolising enzymes and the efficiency of methylation processes. The existence of such relationships is confirmed by the publications of Gonzales-Martinez et al. (2020) and Kazenifar et al. (2020).

Biotransformation rate (i.e. methylation of arsenic species) has a major influence on arsenic tumorigenicity. The methylation patterns of arsenic have been reported to be potentially affected by genetic polymorphisms (ASMT3 polymorphisms) and epigenetics. Besides, increased KEAP1 and Nrf2 mutations and polymorphisms of NADPH oxidase may increase ROS[2]-mediated carcinogenic and cardiovascular effects of arsenic, respectively.

Similar relationships have previously been confirmed in a population of workers chronically exposed to arsenic compounds. The magnitude of arsenic exposure has been shown to correlate closely with the degree of DNA methylation (Janasik et al. 2018). It has also been shown that the concentration of iAs or the sum of iAs + MMA in urine can be a reliable biological indicator of occupational exposure to arsenic. Some studies demonstrated that As3MT and/or GSTs genotype may influence As metabolism (Janasik et al 2015, Ladeira, C., & Viegas, S. 2016)

The concentrations of total arsenic and iAs, MMA and DMA are all fairly constant over time with small intra-individual variabilities.

In the HBM4EU Aligned Studies, arsenic species in urine have been measured in teenagers. The above-mentioned mutations and polymorphisms have however not been assessed and hence not linked to arsenic exposure.

Concerning the studies compiled before HBM4EU, no data on genetic polymorphisms are available that have not been published yet. Stajnko et al. 2019 reported on polymorphisms in the Slovenian Phime-Crome cohort.

6 What are possible health effects resulting from chronic low exposure to arsenic from food consumption?

A causal association between human arsenic exposure and lung, skin, and bladder cancer has been recognized. The strength of evidence of causal associations with ischemic heart disease and cardiovascular disease, hypertension, stroke, diabetes, skin lesions, and effects on pregnancy outcomes (foetal and infant morbidity, foetal loss, stillbirth, and neonatal mortality) is also considered to be robust.

Causal associations with liver and kidney cancer, non-malignant respiratory disease, neurodevelopment, and effects on the immune system are less certain. A scoping review evaluating the link between arsenic exposure and asthma in epidemiological studies only found a potential association. US EPA is currently performing an in-depth investigation of the shape of the dose-response curves in the low dose region. The scientific community has not yet agreed whether it is possible or not to define a threshold for the carcinogenicity of arsenic.

2 ROS = Reactive oxygen species, are highly reactive chemicals formed from oxygen.

7 What is the safe intake level for arsenic that is without any appreciable health risk in the general European population?

HBM4EU has identified that an important fraction of the population in the EU is at risk from internal exposure to iAs. Between 15.6 and 52.0% of study participants exceeded the biomonitoring equivalent set as a guidance value to prevent adverse effects (hyperpigmentation and vascular complications).

The daily intake dose of iAs that was estimated based on average HBM levels from HBM studies and kinetic modelling (0.16 µg kg-1 bw/day) corresponded to a lifetime excess lung cancer risk of $2.7x10^{4}$.

There are no relevant tolerable intakes or reference doses by which to assess safety of either inorganic or organic arsenic in the diet. Inorganic arsenic is genotoxic and a known human carcinogen. Until more scientific information becomes available about the effects at low doses, exposure to inorganic arsenic should be as low as reasonably practicable, and no safe levels are considered.

8 How can harmonised, validated and comparable information be collected to support and evaluate current policies?

As the HBM4EU Aligned Studies showed an association of arsenic exposure with seafood and rice intake and the exceedance of BE-values, policy action could aim at reducing rice or rice-based products intake in children.

It is also recommended to strive for more upfront harmonization, more representative studies, and inclusion of additional age groups in future EU-wide initiatives.

9 How can HBM4EU results support European policy decisions?

Harmonised data collection in support of current policies would best be achieved, if there were obligatory reporting requirements for human biomonitoring data.

The HBM data demonstrate that iAs levels are too high, however more knowledge on sources, reduction measures and surveillance is needed.

Therefore, establishing a permanent European arsenic biomonitoring system in support of arsenic-related European policies would be of value.

KNOWLEDGE GAPS

HBM4EU has helped to identify several specific data gaps that are needed to provide policymakers relevant and strategic data to establish appropriate regulations and improve chemical risk management.

However, some gaps will remain after the end of HBM4EU which should be addressed in the future:

- Assessment of the role of genetics in contributing to the population's variability in sensitivity to the adverse effects of arsenic.
- Assessment of health effects of chronic exposure at low doses as currently measured in the population.
- Assessment of exposure from drinking water with concentrations below the limit and dietary arsenic intake for the general European population.

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