Substance report

June 2022

Arsenic

HBM4EU science and policy for a healthy future

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Glossary

Abbreviations	
C&L	Classification and Labelling
CLP	The ‘Classification, Labelling, Packaging’ Regulation Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures.
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
HBM	Human Biomonitoring
HBM4EU	European Human Biomonitoring Initiative
IARC	International Agency for Research on Cancer
OEL	Occupational Exposure Limits
REACH	The ‘Registration, Evaluation, Authorisation and Restriction of Chemicals’ Regulation Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
WP	Work package

1 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

2 Introduction

HBM4EU is a project funded under Horizon 2020 and runs from 2017 until June 2022. It generates knowledge to inform about the safe management of chemicals, and hence protect human health in Europe. HBM4EU uses human biomonitoring (HBM) to monitor the actual human exposure to chemicals and resulting health impacts to build upon existing evidence bases and improve chemical risk assessment. HBM4EU compares data from across Europe which allows an understanding of regional differences and can help to identify vulnerable groups in order to inform targeted measures to reduce exposure. The results of the HBM4EU project are aimed at supporting policy development, by providing a key evidence base in the understanding of exposure and impacts to toxic chemicals.

If you would like to read more about the project itself, please visit the HBM4EU website.

2.1 How to use this document

This document provides a summary of the known and suspected adverse human health effects of arsenic and describes the main exposure pathways for humans. It also indicates where HBM could be of value in the development of EU policy, along with the remaining challenges in determining human arsenic exposure. This substance report is intended to inform scientists, relevant stakeholders and policy makers on the value of HBM to establish the EU population's exposure to arsenic.

This substance report is based largely on the HBM4EU scoping document for arsenic, first draft produced in 2019 and updated regularly, as well as the accompanying reports on legislative mapping and policy questions. Where necessary, additional information has been used from the European Chemical Agency (ECHA) documents including the classification and labelling (C&L) Inventory, and legislative text for relevant EU policy areas, have also been used for this brief.

2.2 Overview of arsenic

Arsenic is a metalloid[2] that occurs naturally in the earth's crust and is considered as a significant environmental toxicant. The presence of arsenic in the environment is further increased through anthropogenic activities such as mining and combustion of fossil fuels such as coal (Mandal and

[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.
[2] Metalloids are chemical elements that have properties of metals and nonmetals.

Suzuki, 2002). While naturally occurring arsenic can be found largely locked away within the earths soil and geological layers; anthropogenic sources of arsenic are emitted into air, water, and soil where the pathway to environmental species, ecosystems and humans is more direct. This further underscore arsenic's role as an environmental toxicant and man's role as a mechanism for human exposure. Based on a 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 (such as arsanilic acid and methylarsonic acid) or inorganic (such as arsenic trioxide and sodium arsenite). This policy brief refers to its inorganic form as this poses the greatest risk for human health due to its higher toxicity and is furthermore the form which predominates as an environmental contaminant.

Arsenic (CAS 7440-38-2) is registered under the EU REACH[3] Regulation in the 100 – 1 000 tonne per annum bracket. Arsenic is primarily used in alloys of lead (e.g., batteries) and semiconductor electronic devices, but it is also used in the production of pesticides, wood treatment products and medicines for e.g., the treatment of a form of uncommon blood cancer (Grund et al., 2008).

3 Human exposure to arsenic

An overview of main sources of exposure (environmental, occupational, consumer) and exposure pathways (oral, inhalation, dermal) are provided in Figure 3.1.

Additional information on these sources and pathways is also provided in Appendix 1.

The main source of arsenic exposure for the general population is through the diet and drinking water. Additionally, exposure from occupational settings may be significant for certain individuals or groups depending on the specific settings for manufacture and use.

3.1 Environmental exposure

Arsenic naturally occurs in rocks and, to a greater extend, in soils (Mandal and Suzuki, 2002). Due to anthropogenic activities such as mining and burning of coal, arsenic is then further released at the surface level of the earth. As arsenic is persistent and can be detected in soils after more than 15 years, environmental contamination is a serious threat (Merwin et al., 1994). The concentrations of arsenic in soil varies geographically.

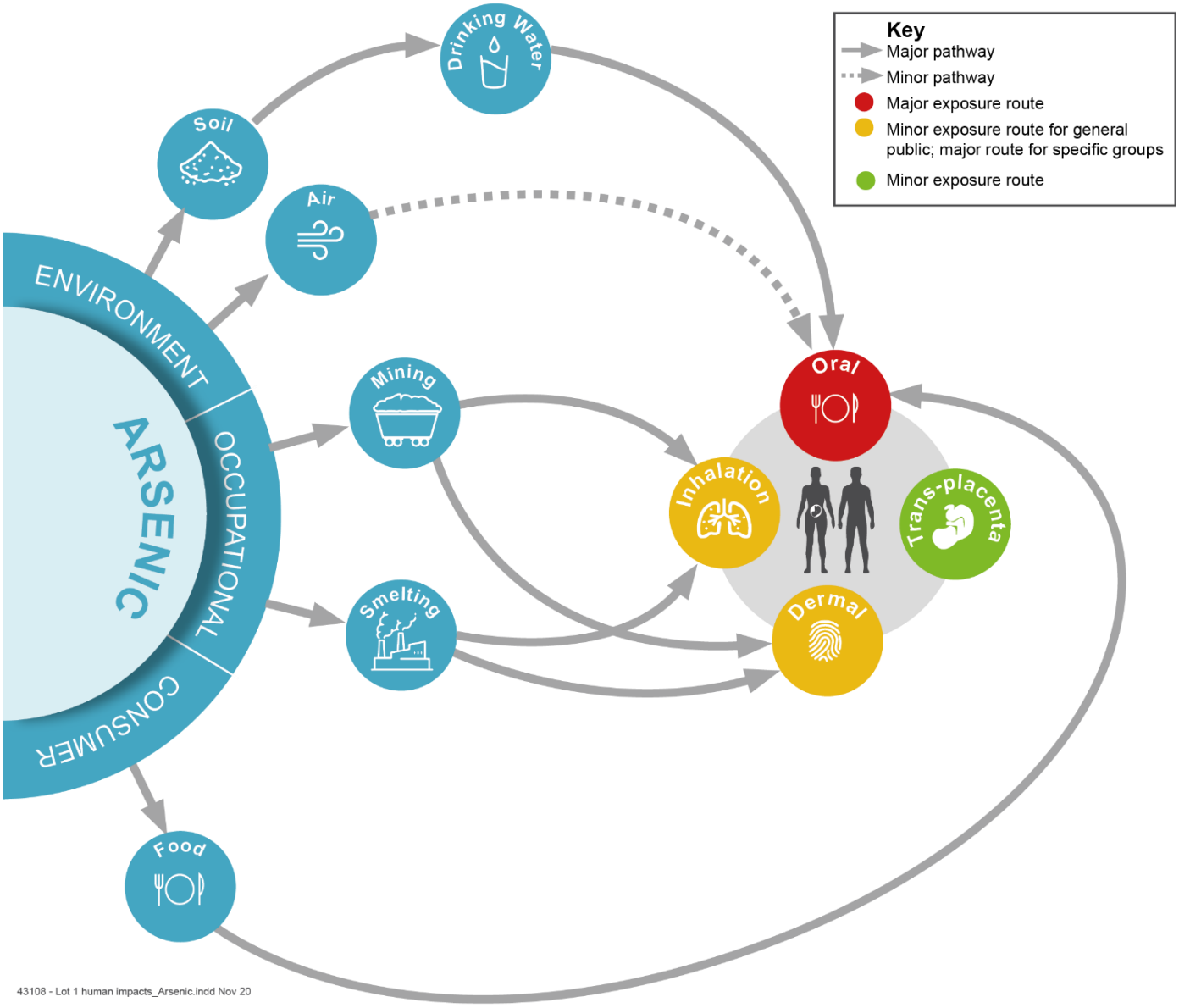
Arsenic is found at low concentrations in natural ground water (< 10 g/L); but concentrations increase significantly in mining areas (100 – 5 000 g/L) (Mandal and Suzuki, 2002). The WHO and United States EPA have set recommendations for drinking water which should not exceed 10 µg/L of arsenic. According to the WHO, at least 140 million people worldwide are exposed to drinking water containing arsenic above the recommended maximum (WHO, 2019). The knowledge on arsenic levels in drinking water and associated health impacts is limited. According to the Joint FAO/WHO Expert Committee on Food Additives (JECFA), evidence on adverse health impacts is stronger for concentrations above 50 µg/L. There are limited EU studies on the exposure through drinking water with concentrations below the limit available. It can be concluded that exposure through drinking water may be a more important exposure source for non-European populations.

Atmospheric concentrations of arsenic in the EU are considered low. However, geographical differences due to the extent of industrial activities occur. In 2000, arsenic levels were up to 1.5

[3] The Regulation on the Registration, Evaluation, Authorisation, and restriction of Chemicals. EC 1907/2006.

ng/m^3 in rural areas, up to 3 ng/m^3 in urban areas and no more than 50 ng/m^3 in industrial areas (European Commission, 2000).

Figure 3.1 Overview of exposure routes and pathways for arsenic



3.2 Occupational exposure

Workers in industries such as gold and copper mining, smelting operations, arsenic production, wood preservation and glass manufacturing may be exposed to arsenic through inhalation and dermal contact. HBM methods to monitor different arsenic forms with regards to occupational exposure are available (Janasik et al. 2014, Appostoli et al., 1999, Hakala and Pyy, 1995). Further, ISO11041:1996 provides a guideline to determine particulate arsenic in workplace air[4].

[4] https://www.en-standard.eu/iso-11041-workplace-air-determination-of-particulate-arsenic-and-arsenic-compounds-and-arsenic-trioxide-vapour-method-by-hydride-generation-and-atomic-absorption-spectrometry/

3.3 Consumer exposure

The general public in the European Union are predominantly exposed to arsenic through food as it accumulates in plant and animal tissues after it has been released from anthropogenic activities such as mining. Due to their relatively high consumption, the following food products are of concern: milk (0.05 µg/kg bodyweight per day), wheat bread (0.06 µg/kg bodyweight per day), soft drinks (0.13 µg/kg bodyweight per day), beer (0.25 µg/kg bodyweight per day) and drinking water (0.08 µg/kg bodyweight per day). Further, rice (brown 0.38 µg/kg bodyweight per day), crustaceans (0.06 µg/kg bodyweight per day) and molluscs (0.11 µg/kg bodyweight per day) are of concern as they contain high levels of arsenic. (EFSA 2014). If you would like to read more about regulations on arsenic in food products, please refer to Section 5 of this brief.

4 Health impacts of arsenic

4.1 Overview of key health impacts from arsenic

The human health effects due to the exposure to arsenic are presented in Figure 4.1. It becomes evident that the main health impact caused by arsenic is cancer. Other impacts are suggested but reliable data to validate suspected effects is missing.

Susceptibility to the toxic effects of arsenic varies considerably between individuals and populations depending on variations in individuals' metabolism related to factors such as age, gender, 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 in identifying impacts.

An overview of current EU (ECHA C&L Inventory) classification of arsenic is provided in the table below. If you would like to read more about arsenic, please visit the referenced ECHA info card in Table 4.1.[5]

Table 4.1 Overview of CLP classifications for arsenic

Substance	Properties of concern				Category according to CLP criteria								ECHA info card
	Carcinogenicity	Endocrine Disrupting (ED)	Skin sensitising (SS)	Persistent, Bioaccumulative and Toxic (PBT)	Carcinogenicity	Acute Toxicity	Specific target organ tox (repeated exposure)	Specific target organ tox (single exposure)	Reproductive Toxicity	Mutagenic	Eye Damage/ Eye Irritation	Skin Corrosion/ Irritation	
Arsenic					1A 1**	3*	2	3	2	2	1	2	Link

* Harmonised classification under the CLP Regulation. (Other classifications are those notified to the CLP inventory but without harmonised EU classification.); ** Based on IARC classification. Blank cells denote a lack of classification.

[5] An explanation of the categorisation of the strength of evidence for the health effects presented in Figure 4.1 is provided in Appendix 2.

Figure 4.1 Overview of health effects associated with exposure to arsenic

Target organ of the body	Effects	Relevant Substances	Adults (men)	Adults (women)	Infants / Foetuses
Organ specific/ whole body	Cancer (skin, lung, bladder, liver and kidney)	Arsenic	●	●	●
Prostate	Cancer	Arsenic	●	○	●
Brain/ neurological system	Disturbance of neurodevelopment	Arsenic	○	○	●
Cardiovascular System	Cardiovascular diseases such as hypertension	Arsenic	●	●	●
Metabolism	Abnormal glucose metabolism and type II diabetes	Arsenic	●	●	●
DNA	DNA damage	Arsenic	●	●	●
	Reproductive toxicity	Arsenic	●	●	●

Key: ● Strong evidence ● Suspected ● Evidence lacking ○ Not applicable

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4.2 Vulnerable target groups

Children are the most vulnerable and sensitive group to the adverse effects of arsenic. The dietary exposure for children under three-year olds is in general estimated to be about 2 to 3-fold higher than that of adults as children have higher (food) intake per kg body weight. In addition, pregnant and lactating women and hence, foetuses may be more vulnerable and sensitive to the effects of arsenic as these are the periods of the human brain development. There has also been a growing body of evidence since the early 2000s of the potential for pre-natal effects of arsenic, and possible transplacental exposure (Farzan, 2013; Young et al., 2018; ATSDR, 2007; and ATSDR, 2016 update to toxicological profile).

4.3 Societal concerns

Societal concerns are mainly related to arsenic levels in food and drinking water and the associated adverse health impacts. The WHO included arsenic in the WHO's 10 chemicals of major public health concern and demands more scientific attention. Arsenic is part of the new 2030 Agenda for Sustainable Development by the WHO/UNICEF Joint Monitoring Programme for Water Supply, Sanitation and Hygiene. If you would like to read more about the WHO's work on arsenic, please visit their website.

The NGO Chemsec (International Chemical Secretariat) is seeking for the substitution of toxic chemicals and advocates for more progressive chemical legislation. Chemsec has included arsenic in the SIN (Substitute It Now) List which comprises chemicals that have adverse health impacts. If you would like to read more about the list, please click here.

Arsenic ranks first out of 275 substances on the "2019 Substance Priority List" by the Agency for Toxic Substances and Disease Registry (ATSDR). The list prioritises substances based on their frequency, toxicity, and potential for human exposure. If you would like to read more about the list, please visit the website of the ATSDR.

5 EU policies on arsenic

Several policy measures have already been introduced in the EU to address human exposure to arsenic and managing risks. In general, the existing EU policies cover i) regulations on chemicals; ii) consumer products; iii), the environment and iv) occupational exposure. An overview of these regulatory measures at EU level is provided in Table 5.1.

Table 5.1 Overview of EU policies relating to arsenic

Chemicals	• Arsenic is registered under REACH (Regulation (EC) No 1907/2006), with specific uses further controlled under Annex XVII (restriction). • Arsenic 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) – see list of classifications above.	• Maximum levels for arsenic in certain foods have been established by Regulation (EC) No 2015/1006 (e.g. rice waffles 0.30 (µg/kg).	**Consumer**
Environmental	*Water* • The Drinking Water Directive (98/83/EC) limits the concentration of arsenic in water for public consumption to 10 µg/L. *Air* • Directive (EU) 2016/2284 on the reduction of national emissions of certain atmospheric pollutants requires Member States to report arsenic pollution annually.	• 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/m^3) for arsenic applies from 11 July 2023 for the copper smelting sector.	**Occupational**

6 Policy questions for arsenic

6.1 Introduction

For each of the HBM priority substances stakeholders were asked to identify policy related questions that HBM4EU should address in order to contribute to the strengthening of policy ambitions on arsenic. Further background detail on arsenic and how the policy questions were selected is available in the scoping document and the report on stakeholder consultation and mapping of needs.

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

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 6.4µg/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 arsenobetaïne concentrations are in the range of 0.39-8.28 µg/g crt and 17.88-128.02 µg/g crt, respectively.

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

In the HBM4EU Aligned Studies, arsenic has been assessed in 6 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.

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

Current exposure of the average EU population to arsenic from drinking water is low due to the limited presence of iAs in drinking water. The main source of iAs is diet, especially rice and other cereals, juices and seafood. Average exposure levels (daily doses) calculated from food intake 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 main iAs intake of the general population is through dietary exposure.

The analyses in the HBM4EU Aligned Studies focus on 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 all cohorts of teenagers included in the analyses.

6.5 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.

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 % of study participants exceeded the Biomonitoring Equivalent set as a guidance value to prevent adverse effects (hyperpigmentation and vascular complications).

Sex and 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 (including from 11 to 1737 participants exposed to “normal” levels of iAs), and kinetic modelling corresponded with a lifetime excess lung cancer risk of 2.7 x 10-4. Credible justification of assumptions, necessary to assure the credibility of such calculation, was beyond the scope of this work, therefore, the calculated value must be interpreted with caution. The approach can be considered as conservative, overestimating the risk especially at low exposure levels.

The magnitude of toxic manifestations of arsenic is influenced by individual characteristics such as age, gender, nutritional status, genetic factors, lifestyle, and the presence of other diseases. Many of these characteristics can affect the toxicity of arsenic via their impact on the metabolic pathway. In general, population-based investigations show that the male populations have a lower methylation capacity, which could make them more susceptible to arsenic toxicity than females. Highly effective methylation during infancy has also been observed, which may also be related to the effect of estrogen and folate donors on arsenic methylation.

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.

6.6 What factors (genetic polymorphisms) make people more susceptible or not to the risk of health effects due to arsenic exposure? Which are the best and most sensitive biomarkers for reliable identification of arsenic exposure and how can they be linked to potential adverse health-effects?

As reported in AD13.6, preferred biomarkers are determination of arsenic and its chemical forms in urine. The sum of As(III), As(V), MMA, and DMA correlates well with drinking water concentration or estimated daily dose calculated using drinking water concentrations. The concentrations of total arsenic and iAs, MMA, and DMA are all fairly constant over time with small intra-individual variabilities. First morning voids of total arsenic are indicative of and correlated with subsequent voids throughout the day. For these reasons, speciated arsenic in urine (iAs III, iAs V, MMA, and DMA) are the preferred biomarker(s) for exposures to inorganic arsenic. Urinary DMA is widely included as one of the markers of iAs exposure. However, it can also be excreted in urine after direct ingestion or after ingestion of less toxic arsenosugars and arsenolipids hence overestimating the exposure to iAs.

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-mediated carcinogenic and cardiovascular effects of arsenic, respectively.

In 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 (https://doi.org/10.1016/j.envres.2018.11.045) reported on polymorphisms in the Slovenian Phime-Crome cohort.

6.7 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 (fetal and infant morbidity, fetal 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 only found a potential association in epidemiological studies. 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.

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

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

Also, we recommend striving for more upfront harmonization, more representative studies, and inclusion of additional age groups in future EU-wide initiatives.

6.9 How can harmonized, validated and comparable information be collected to support and evaluate current policies?

The use of the ICP-MS technique in combination with separation techniques, e.g. HPLC, now appears to be the most advantageous analytical technique to use in the As exposure assessment. Under WP9 activities, laboratories invited to participate in proficiency testing were qualified based on QA/QC checks carried out. Currently, the proficiency tests are completed, 2 laboratories that have successfully passed the controls are included in the list of laboratories performing the tests in the assessment of the second list of priority substances.

6.10 How can HBM4EU results support European policy decisions?

The policy relevance of the results has been addressed in answers to specific policy questions mentioned above.

7 HBM4EU outputs to date

7.1 Categorisation

Substances under HBM4EU have been categorised depending on availability of HBM data. The categorisation indicates the information gaps allowing the development of targeted activities to fill the knowledge gaps. Substances will pass from Category E over D, C, B towards Category A as more information becomes available. Fully characterised substances should end up as category A substances.

Table 7.1 Categorisation of arsenic

Category		Priority substance(s)	Details
B	HBM data exist but not for across Europe	Arsenic and inorganic compounds	The exposure pathways are identified. First studies on health impacts have been conducted but greater knowledge is needed. HBM data for arsenic as a food and drinking water contaminant are available, but at insufficient level to provide an overall picture of exposure in Europe.

7.2 Key outputs

Current exposure

In order to further support current and future HBM studies, HBM4EU developed a variety of publicly available groundwork materials for a harmonised approach to study planning and conduct in Europe (WP7, HBM4EU online library). For arsenic species, questionnaires for adults and adolescents are available.

Definition of the best biomarkers, matrices and analytical methods for monitoring arsenic and arsenic species in human samples.

A list of approved laboratories carrying out analyses of arsenic in urine and their inclusion in the European network of HBM laboratories.

A prioritised list with most suitable biomarkers, matrices and analytical methods has been produced (WP9, D9.7). Interlaboratory assays (ICI/EQUAS) have been organised for measurement of arsenic species in urine, as this was considered most appropriate. Chemical analyses of arsenic have been improved. A total of 3 laboratories participated in the ICI/EQUAS. There are 2 qualified laboratories (WP9, D9.8).

A sampling frame has been established to align the planning of ongoing/planned studies to collect HBM data of the prioritised chemicals (including bisphenols) with EU wide coverage (WP8, D8.3).

The HBM4EU Aligned Studies (2014-2018) have measured arsenic (6 markers: Total arsenic (As), arsenic(3+) (As III), arsenic(5+) (As V), monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), and arsenobetaine (Asb)) in urine samples from teenagers between 12 and 18 years of age from 6 different sampling sites in Europe (Sweden, Spain, Slovenia, France, Belgium and Germany) representing 1445 individuals.

A specific statistic data analysis plan for arsenic has been elaborated (WP10).

A research protocol has been developed under the activities of WP 10 (Task 10.4) on the possibility of using available studies related to the As exposure. From the available data, prior to HBM4EU sampling frame, 30 studies in adults, adolescents, children and pregnant women were identified. Based on the diversity in study design, sampled matrices, sampling periods, sampled age groups, it was decided to not further use these studies to answer policy questions

Biomonitoring

WP7 collected information on existing, ongoing and planned general and occupational HBM studies in the HBM4EU consortium in an easily accessible tool providing up-to-date information.

The European HBM dashboard provides summary statistics for HBM data from different European countries, with 14 aggregated datasets. In IPCHEM (Information Platform for Chemical Monitoring), metadata for 30 datasets are available. It consists of studies in new-borns and their mothers, in children, in teenagers, and in adults. The studies measured arsenic in (cord) blood, breast milk, and/or urine. One data collection is included that measured arsenic in brain, bone, liver, kidney and lung tissue.

Studies that assessed the different arsenic species are limited.

The HBM4EU Aligned Studies (2014-2018) have measured arsenic (6 markers: Total As, As III, As V, MMA, DMA, Asb) in urine samples from teenagers between 12 and 18 years of age from 6 different studies in Europe (Sweden (Riskmaten Ungdom), Spain (BEA), Slovenia (CRP), France

(Esteban), Belgium (FLEHSIV) and Germany (GerES)) representing 1445 individuals. Not all biomarkers were analysed in all contributing studies, therefore the number of sampling sites and data points can vary per biomarker.

Geographical spread

A critical review of the existing scientific literature was performed. In Europe there are several hotspots of arsenic contamination, including Hungary, Croatia, Finland and Spain. In these regions, arsenic exposure is mainly related to the type (thermal, drinking) and content of water. Maximal As concentrations were found to be between 8 and 8000 µg/l. Poland is an area where exposure to As in some regions depends on industrial emissions (above 10 µg/m3).

In the HBM4EU Aligned Studies, the geographic spread of the current exposure has not been assessed, due to the limited number of studies available for Northern, Eastern, Southern, and Western Europe. The statistical analyses in the HBM4EU Aligned Studies focus on differences in exposures based on diet.

Concerning the studies compiled before HBM4EU, geographical spread could not be assessed due to the diversity in study design, sampled matrices, analytical techniques, sampling periods, and sampled age groups.

T5.3 summarized recent work related to background levels of inorganic arsenic (iAs) in food and environment in the European Union (EU). Most data included were from studies from 2000 until 2020. Exposure of different population groups was calculated by combining intake and iAs concentrations of food items to obtain daily doses. A conservative approach was used for iAs bioavailability, i.e. assumed to be 100%.

Vulnerable population

The HBM4EU Aligned Studies (2014-2018) have measured arsenic (6 markers: Total As, As III, As V, MMA, DMA, Asb) in urine samples from teenagers between 12 and 18 years of age from 6 different sampling sites in Europe (Sweden, Spain, Slovenia, France, Belgium and Germany) representing 1445 individuals.

The European HBM dashboard provides summary statistics for studies measuring arsenic exposure in newborns and their mothers, in children, in teenagers, and in adults.

Risk assessment based on HBM data for arsenic has been performed by T5.3. iAs daily doses were calculated from urine iAs metabolites by reverse dose calculation. Daily iAs dose estimates were used for the assessment of cancer risks – based on dose-response relationship proposed by JEFCA (2011) and ECHA (2013) (WP5, D5.8).

WP13 performed a brief literature survey to provide an up-to-date summary of mechanisms of action and susceptibility factors.

Health risks

WP13 performed a brief literature survey to provide an up-to-date summary of mechanisms of action and susceptibility factors.

WP 13 (Task 13.2) and WP14 groups have coordinated the selection of biomarkers of effect according to their utility in human studies, the identification of needs for the implementation of both classical and novel biomarkers of effect and the decision criteria for their validation.

Effect biomarkers for cancer, metabolic syndrome and diabetes, cardiovascular effects, and neurobehavioral endpoints were identified by a comprehensive literature search and consultation of the AOP-Wiki (WP14, D14.5/6 ‘Selection criteria and inventory of effect biomarkers for the 2nd set of substances’).

As part of the assessment of potential effects of various chemical compounds, including arsenic, human health, a publication was prepared entitled "Arsenic and human health. "Scoping review - the association between asthma and environmental chemicals".

WP13 and WP14 performed brief literature searches to provide an up-to-date summary of health outcomes associated to arsenic exposure.

In search of the interdependencies between the exposure and health effects and new specific effect biomarkers, in task 12.3, parameterisation of the PBTK model was performed.

The work performed within this task was presented in "AD12.10 - Report on parameterisation of the second set of priority substance"

Data from 4 studies compiled before HBM4EU are used to study the effects of arsenic exposure on birth weight, gestational diabetes, and maternal blood pressure. This will enable to estimate changes in effect for increasing exposures within the observed exposure range. This will indicate whether the observed exposure levels are a reason for health concerns for new-borns and their mothers.

Analytical methods

The determination of arsenic in biological specimens requires sensitive analytical methods, performed under good quality control conditions. Due to the possibility of separating the different chemical forms that are relevant in the toxicity assessment, it was considered that the assessment of the different forms alongside total arsenic would be the most advantageous biomarker in the exposure assessment.

The HBM4EU Aligned Studies (2014-2018) have measured arsenic (6 markers: Total As, As III, As V, MMA, DMA, Asb) in urine samples from teenagers between 12 and 18 years of age from 6 different sampling sites in Europe (Sweden, Spain, Slovenia, France, Belgium and Germany) representing 1445 individuals.

This is supported by the materials developed in WP7 (see question 1).

Policy decisions

The results of the project will identify stakeholder groups, prioritise the assessment of exposure to chemicals and meet the needs for biological monitoring research for stakeholders, starting with policy makers and researchers.

7.3 Key data gaps

HBM4EU is a five-year project, that kicked off in 2017 and will run until June 2022. HBM4EU has helped to identify a number of specific data gaps that are needed to give policy makers relevant and strategic data to establish appropriate regulations and improve chemical risk management. However, some gaps and needs for action will remain after the end of HBM4EU which should be addressed in the future:

- Selecting and harmonising of exposure biomarkers.
- Assessment of the role of genetics in contributing to the population's variability in sensitivity to the adverse effects of arsenic.
- Assessment of exposure to drinking water with concentrations below the limit and dietary arsenic intake for the European general population.

8 Future recommendations

Despite data on the content of As in food products, there is very little data on health effects. As a result, exposure levels for iAs with no appreciable health risk, i.e. a tolerable daily or weekly intake,

cannot be identified. Therefore, such research is necessary. However, it is known that iAs is genotoxic carcinogen hence there is no safe treshold. Therefore conclude that exposure to inorganic arsenic should be as low as reasonably practicable.

For this reason, there should be extensive studies of the general population (with special attention to the child population) exposed to low concentrations of arsenic in drinking water (less than 10 mcg/l). Further studies of the arsenic content of food products, especially foods for infants and young children, are needed, as the health effects that may be caused by long-term exposure to this element.

9 References

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Appendix 1: Additional information on exposure

Source of exposure	References
Environmental • Arsenic occurs naturally in rocks and soils. • Low concentrations can be found in natural water. • It is released to air, water, and soil through man-made sources.	Mandal B.K., Suzuki K.T. (2002) Arsenic round the world: a review, Talanta 58, pp 201-235
Occupational • Workers in industries such as gold and copper mining, smelting operations, arsenic production, wood preservation and glass manufacturing may be exposed.	Apostoli P, Bartoli D, Alessio L, Buchet JP (1999) Biological monitoring of occupational exposure to inorganic arsenic. Occup Environ Med 56:825–832. doi:10.1136/oem.56.12.825
Consumer • Arsenic is used in alloys of lead and semiconductor electronic devices, but it is also used in the production of pesticides, treatment wood products and medicines for e.g., the treatment of a form of uncommon blood cancer. • Food and drinking water can be contaminated with arsenic.	Grund, Sabina C.; Hanusch, Kunibert; Wolf, Hans Uwe, (2008) "Arsenic and Arsenic Compounds", Ullmann's Encyclopedia of Industrial Chemistry, Weinheim: Wiley-VCH, doi:10.1002/14356007.

Route of exposure	References
Oral • Primary source of human exposure to arsenic is the diet. • Major route of exposure for the general population.	European Food Safety Authority (EFSA) 2014 Dietary exposure to inorganic arsenic in the European population doi: 10.2903/j.efsa.2014.3597EFSA Journal 2014;12(3):3597
Dermal • Dermal uptake of arsenic may occur in industrial processes. • Minor route of exposure for the general population but can be more significant in specific occupational settings.	Apostoli P, Bartoli D, Alessio L, Buchet JP (1999) Biological monitoring of occupational exposure to inorganic arsenic. Occup Environ Med 56:825–832. doi:10.1136/oem.56.12.825
Inhalation • Inhalation of arsenic may occur in industrial processes. • The general population this is not a significant risk since the levels of arsenic in outdoor air are usually very low. • Minor route of exposure for the general population but can be more significant in specific occupational settings.	Apostoli P, Bartoli D, Alessio L, Buchet JP (1999) Biological monitoring of occupational exposure to inorganic arsenic. Occup Environ Med 56:825–832. doi:10.1136/oem.56.12.825
Trans-placenta • Arsenic might cross the placenta and results in foetal exposure. • Possible major route of human exposure.	ATSDR. 2007. Toxicological profile for arsenic (Update). U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp2-p.pdf. January 23, 2015.

Appendix 2: Additional information on health effects

Human health effect	Category	Justification for category	References
Skin (cancer)	Strong	Based on IARC listing of 1	See table 4.1
Lung (cancer)	Strong	Based on IARC listing of 1	See table 4.1
Bladder (cancer)	Strong	Based on IARC listing of 1	See table 4.1
Liver (cancer)	Strong	Based on IARC listing of 1	See table 4.1
Kidney (cancer)	Strong	Based on IARC listing of 1	See table 4.1
Prostate (cancer)	Strong	Based on IARC listing of 1	See table 4.1
Brain/neurological development (disturbance of neurodevelopment)	Suspected	As noted in the scoping document – neurodevelopmental toxicity of arsenic is suggested.	Scoping document NRC (2014)
Cardiovascular system (cardiovascular diseases such as hypertension)	Suspected	As noted in the scoping document – cardiovascular diseases are suggested.	Scoping document NRC (2014)
Metabolism (abnormal glucose metabolism and type II diabetes)	Suspected	As noted in the scoping document – an abnormal glucose metabolism and type II diabetes are suggested.	Scoping document NRC (2014)
DNA (DNA damage)	Suspected	Based on listing of 2	See table 4.1
DNA (reproductive toxicity)	Suspected	Based on listing of 2	See table 4.1

For the categorisation of the strength of evidence for human health effects, the following criteria has been used:

- **Strong –** where the health effect is confirmed by either a harmonised classification indicating that there is a known effect (e.g. 1A or 1B for CMRs) (see Table 4.1), or where there is no applicable C&L classification, a statement in the Scoping Document that concludes there is strong evidence (or where a significant body of evidence is presented in the scoping document).
- **Suspected –** where there is either (a) a harmonised classification indicating that there is a suspected effect (e.g. category 2 CMRs or similar); (b) notified classification for that effect, or

(c) where there is no applicable C&L classification, a statement in the Scoping Document (or other references presented in the Table above) that there is a suspected health impact.

- **Evidence lacking –** where a health effect is noted in the Scoping Document (or other evidence sources referenced in the Table above), but it is stated that evidence is currently lacking or there are uncertainties or inconsistencies in the available evidence.
- **Not applicable –** where a health effect does not apply to a specific group/gender