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Human urinary arsenic species, associated exposure determinants and potential health risks assessed in the HBM4EU Aligned Studies

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ABSTRACT

The European Joint Programme HBM4EU coordinated and advanced human biomonitoring (HBM) in Europe in order to provide science-based evidence for chemical policy development and improve chemical management. Arsenic (As) was selected as a priority substance under the HBM4EU initiative for which open, policy relevant questions like the status of exposure had to be answered. Internal exposure to inorganic arsenic (iAs), measured as Toxic Relevant Arsenic (TRA) (the sum of As(III), As(V), MMA, DMA) in urine samples of teenagers differed among the sampling sites (BEA (Spain) > Riksmaten adolescents (Sweden), ESTEBAN (France) > FLEHS IV (Belgium), SLO CRP (Slovenia)) with geometric means between 3.84 and 8.47 μg/L. The ratio TRA to TRA + arsenobetaine or the ratio TRA to total arsenic varied between 0.22 and 0.49. Main exposure determinants for TRA were the consumption of rice and seafood. When all studies were combined, Pearson correlation analysis showed significant associations between all considered As species. Higher concentrations of DMA, quantitatively a major constituent of TRA, were found with increasing arsenobetaine concentrations, a marker for organic As intake, e.g. through seafood, indicating that other sources of DMA than metabolism of inorganic As exist, e.g. direct intake of DMA or via the intake of arsenosugars or -lipids. Given the lower toxicity of DMA(V) versus iAs, estimating the amount of DMA not originating from iAs, or normalizing TRA for arsenobetaine intake could be useful for estimating iAs exposure and risk. Comparing urinary TRA concentrations with formerly derived biomonitoring equivalent (BE) for non-carcinogenic effects (6.4 μg/L) clearly shows that all 95th percentile exposure values in the different studies exceeded this BE. This together with the fact that cancer risk may not be excluded even at lower iAs levels, suggests a possible health concern for the general population of Europe.

1. Introduction

Arsenic (As) is omnipresent in the environment. In the past it was used in e.g. pesticides and wood treatment products which led to a wide disperse environmental contamination. Local contamination can be found near metal producing/processing industries. Soil arsenic concentrations originating from natural sources are generally lower in Northern European countries compared to Southern (Tarvainen et al., 2013). Local or regional natural hotspots from geological origin exists as

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Abbreviations

As(III)	arsenite
As(V)	arsenate
MMA	monomethylarsonic acid
DMA	dimithylarsinic acid
AB	arsenobetaine
As_{tot}	total arsenic
TRA	toxic relevant arsenic

well (e.g. Cornwall, N-Italy, Hungary), which influence groundwater As concentrations. Untreated well water is sometimes used as drinking water or for e.g. showering, watering of vegetables. Thus, direct intake of well water, which can be relatively rich in As concentrations, or intake of vegetables irrigated with such water, can also lead to substantial human As exposures. Overall, concentrations in drinking water distributed in the EU are well below the WHO provisional guideline value of 10 μg/L (WHO, 2011) which is based on technical limitations rather than evidence from toxicological & epidemiological studies (WHO, 2018). Exceedances of the WHO guideline value are registered in several EU countries, which is mainly due to regional natural hotspots (Van Halem et al., 2009).

Arsenic concentrations in food differ across the EU and are related to concentrations in agricultural soils. Some items that need attention are e.g. cereals (rice), grains and mushrooms because they may contain relatively high As concentrations at weight basis (USFDA, 2022). But also seafood (fish, mollusks, crustaceans, seaweed) and food supplements based on seafood can contain relatively large As concentrations (Gao et al., 2018). However, arsenic in the environment is present as numerous chemical species, differing greatly in properties and toxicity (Francesconi et al., 2002; Hughes, 2002). As species observed in the environment are a. o. inorganic iAs (arsenite As(III), arsenate As(V)), arsenobetaine (AB), methylated arsenic species and organoarsenicals (sugars, lipids). Main sources of iAs human exposure already identified are the use of As containing well water, the consumption of rice and grains (EFSA, 2021). Arsenobetaine, DMA and organoarsenicals were already identified to be present in seafood (Luvonga et al., 2020) with AB the predominant species in finfish and shellfish and arsenosugars and arsenolipids the predominant species in algae (Krishnakumar et al., 2016). Mushrooms contain DMA, AB and some iAs as well (Braeuer and Goessler, 2019).

Overall, iAs is considered as the most toxic arsenic species. In the human body iAs is metabolized to MMA (monomethylarsonic acid) and DMA (dimithylarsenic acid) (Drobna et al., 2009). Opposite, after ingestion of arsenobetaine (AB) rapid excretion without interaction and toxicity in the body is noted (Lai et al., 2004). Further, there is a variation in toxicity of methylated arsenic species, naturally present in food or metabolized after ingestion of inorganic arsenic, arsenosugars and -lipids. As(III) and As(V) are categorized as nonthreshold Class I carcinogens (IARC, 2012), with acute toxicity of LD50 (lethal dose, 50%) = 15–42 mg/kg body mass, while simple methylated arsenicals are deemed to pose intermediary toxicity (LD50 = 890–10600 mg/kg body weight), and the tetraalkylated compound AB, present in fish and the principal dietary source of arsenic exposure for humans, is considered nontoxic with LD50 = >10000 mg/kg body weight and is primarily eliminated intact by humans in urine (Luvonga et al., 2020). After intake of arsenosugars, DMA(V) is the main species after metabolization (Francesconi et al., 2002; Feldmann and Krupp, 2011; Chen et al., 2019). Arsenosugars show less cytotoxicity than MMA or DMA. Structural characteristics (presence of sugar groups) are important and complexes with enzyme sulfhydryls cannot easily be formed (Andrewes et al., 2004). After intake of arsenolipids, biotransformation to possibly toxic species may take place as for arsenosugars (Taylor et al., 2017). Toxicity data on arsenolipids are limited. Arsenohydrocarbons, a subcategory of arsenolipids, show cytotoxicity (Meyer et al., 2014) and have neurotoxic properties (Witt et al., 2017).

When focusing on urinary arsenic, the sum of urinary inorganic arsenic (iAs = As(III)+As(V)) and metabolites MMA (monomethylarsonic acid) and DMA (dimithylarsenic acid) is often used as an indicator for exposure to toxic inorganic arsenic. However, there is increasing evidence that DMA in human urine is not only originating from the metabolization of inorganic arsenic but also results from direct intake or from the metabolization of organic arsenic compounds (Francesconi et al., 2002; Schmeisser et al., 2006; Yusà et al., 2018). According to Luvonga et al. (2020) also arsenosugars and arsenolipids, which are present at higher levels in e.g. seaweeds can be of importance from a toxicological point of view. Recent toxicokinetic studies show that some organoarsenicals are bio-accessible and cytotoxic (Luvonga et al., 2020).

There is a need for harmonization of analytical methods, statistical processing and reporting of HBM-data to enable a sound comparison of exposure-levels, to obtain information on exposure determinants and e.g. time-trends. Therefore, in this manuscript we investigate data of ongoing and newly conducted human biomonitoring (HBM) studies, aggregated and harmonized by HBM4EU for differences and similarities between the different study countries, for common exposure determinants and to compare biomarker levels with existing risk-based guidance values. This study was carried out under HBM4EU, co-financed under Horizon 2020. The main goal of HBM4EU was to coordinate and advance HBM in Europe in order to provide science based evidence for chemical policy development and improve chemical management (Ganzleben et al., 2017). More information is available on the HBM4EU website (www.HBM4EU.eu). The HBM4EU Aligned Studies are a survey aimed at collecting HBM samples and data as harmonized as possible from existing (national) studies or newly conducted studies to derive current internal exposure data for the European population/citizens across a geographic spread (Gilles et al., 2021). Within the HBM4EU Aligned Studies, arsenic was one of the prioritized chemicals. As metabolites were measured in urine samples of teenagers (12-18y). Samples were sometimes analysed in different laboratories but data were quality assured/controlled (QA/QC) following a scheme designed and implemented in HBM4EU (Esteban López et al., 2021).

2. Methods

2.1. Data

2.1.1. Population

Information about the involved HBM studies and the study design can be found in (Gilles et al., 2021). Arsenic data were obtained from Germany (GerES V-sub; 2015–2017), Sweden (Riksmaten adolescents; 2016–2017), Slovenia (SLO CRP; 2018), Spain (BEA; 2017–2018), France (ESTEBAN; 2014–2016) and Belgium (FLEHS IV; 2017–2018). Characteristics of the study participants and ethics can be found in Gilles et al. (2022). Briefly, the age of participants ranged between 12 and 18 years. A 50:50 ratio of male and female participants, with individuals living in rural areas, in towns/suburbs and in cities, and with at least 10% of individuals from low, medium and high educational level (of the household) was a recommendation for the studies. No samples were taken from persons living in known natural or industrial hot spots.

2.1.2. Urinary arsenic concentrations

Urinary measurements of the following arsenic species were collected: As(III): arsenite, As(V): arsenate, MMA: monomethylarsonic acid, DMA: dimithylarsenic acid, AB: arsenobetaine, As_{tot}: total arsenic, TRA: toxic relevant arsenic. In most studies, TRA was calculated as a sum parameter (see further) except in the ESTEBAN study where it was determined by HPLC-ICPMS as a measured sum of species (As(III), As(V), MMA, DMA). Data were normalized for specific gravity (SG) except

for ESTEBAN where data on SG were not available. Biomarker data were normalized as follows:

$$C_{SG} = \frac{C_{bio}\ (1.024 - 1)}{SG - 1}$$

With C_{SG} the biomarker concentration in urine normalized for specific gravity, C_{bio} the wet weight concentration of the biomarker in urine and SG Specific Gravity. The value 1.024 was taken as average urinary specific gravity (Kuiper et al., 2021).

Methodologies for handling data below limits of detection (LOD) or quantification (LOQ) have been a long-recognized issue. Biomarker data are typically left-censored data; data below a LOD/LOQ for which the true value is unknown are often referred to as "left-censored". Depending on the laboratory, the LOD or LOQ was used as lower limit to report measured values. For measurements indicated as below these limits, possible values were randomly imputed by using a truncated lognormal distribution (R statistical analysis software package; R Core Team, 2018). This imputation was only performed if at least 30% of the concentrations had a value above the LOD or LOQ for a specific biomarker per study. Geometric means (GM) were only calculated if at least a quantification rate of 60% was obtained.

Sum parameters (e.g. TRA or toxic relevant arsenic: As(III)+As(V)+ MMA + DMA; mass based) were only calculated if all of the compounds constituting the sum were analysed in a study and if at least one of the compounds was detected for at least 60%. For the construction of sum parameters, values below LOD/LOQ were substituted by LOD/LOQ divided by 2 (as the randomly imputed biomarker data are not always available if detection frequency <30% as described above). LOD and LOQ values and detection frequencies per study are reported in Table A1 (see supplementary material). For the study of ESTEBAN, information on concentrations of different As species was not available. TRA was reported by ESTEBAN as a measured sum of species without giving information on the contribution of the individual As species.

2.1.3. QA/QC

Within the framework of the HBM4EU project, a complete QA/QC programme offering 95 biomarkers was conducted (Esteban López et al., 2021). The programme included an interlaboratory comparison (ICI) for the analysis of arsenic in urine, covering total arsenic, As(III), As(V), MMA, DMA and arsenobetaine, to assess the comparability and reliability of analytical methods across the participating expert laboratories. Three rounds of ICI were performed from February to March 2020. For each round, two different test samples consisting of 5 mL urine spiked with arsenic at two different concentrations were prepared and sent to the participating expert laboratories for single analysis. Homogeneity and stability assessment of the control materials confirmed that the materials were adequately homogeneous and stable. Consensus values were calculated by averaging the values obtained by the expert labs when the relative uncertainty of the mean was within 17.5%. In order to express the proficiency of the laboratories in a numerical way, Z-scores were calculated using the consensus value and a fixed fit-for-purpose relative target standard deviation (FFP-RSDR) of 25%. Three expert laboratories from different countries participated in the ICI.

2.1.4. Questionnaires

Questionnaires used within the new and ongoing HBM campaigns under HBM4EU were harmonized. Questions about socio-demographic characteristics were included in all studies; the majority of studies also captured information on dietary habits and health status of the participant, lifestyle, and residential environment. For some ongoing campaigns questionnaire data needed to be harmonized *post factum*. Therefore, some information may be available in some studies while not in others. For upcoming HBM studies, base and substance specific harmonized questionnaires are described by (González-Alzaga et al., 2022). Specific questionnaires for teenagers have been developed for arsenic and are available in the HBM4EU library for upcoming studies (https://www.hbm4eu.eu/online-library/).

2.2. Statistical analysis

Statistical analyses were performed in SPSS Statistics 28. Descriptive statistics were calculated. Determinants of variability in As concentration were analysed (ANOVA). Variables considered were among others personal factors such as sex and BMI, questions from the questionnaires related to the living environment as exposure to groundwater, questions related to food consumption, information on socio-economic status (SES; categories for equivalent household income and highest education in household), information on degree of urbanization at the home address (see Table 1). The chosen variables were in the first instance based on associations already observed in literature and science based hypotheses about potentially influencing factors. Studies were analysed separately as based on the questionnaires, not all questions were answered in all studies (see Table 1). Arsenic concentrations were normalized for SG and ln transformed. In a first analysis, linear regression was used to identify single variables which might explain differences in As concentrations with matrix (spot urine or first morning urine) and SG forced into the model. Secondly, a multiple linear regression analysis model was built for each ln-transformed biomarker "per study" starting from variables with $p < 0.2$ in the former analysis and backward selection was applied. Only those variables having a significance level of $p < 0.05$ were kept in the final multiple linear regression model. Variables reflecting socio-economic differences can be proxies for other, underlying, determinants of exposure and were added to the models as final steps. For the multiple linear regression model, only the following sum parameter was considered: sum of As(III), As(V), MMA, DMA. A model with and without arsenobetaine as a covariate was built. Arsenobetaine was taken up in the model to correct for seafood intake. A pooled regression analysis with all studies was not performed seeing that not all information from the questionnaires was available in each study. Additionally, a correlation analysis between different As species was performed on ln-transformed non-imputed values for all studies combined.

3. Results and discussion

3.1. Exposure in Europe and associations between as species

Although many efforts were put to obtain quality and comparable results for arsenic and species there were some limitations due to the approach of the aligned studies. All new arsenic analysis under HBM4EU were done in expert laboratories that participated successfully in the QA/QC HBM4EU programme and all of them analysed all the biomarkers under study: total arsenic, As(III), As(V), MMA, DMA and arsenobetaine. However, some studies provided arsenic results that were generated before HBM4EU. For that reason, the results did not cover all the biomarkers in the different studies and the results cannot be considered at the same level of comparability. In those cases, the HBM4EU Quality Assurance Unit requested information related to the analytical method applied, quality control measures, LOQs, etc. in order to assess the quality and comparability of the results. However, since this retrospective assessment cannot ensure the comparability, different labels were assigned to the data: a) biomarker data quality assured by HBM4EU QA/QC program; b) biomarker data generated before HBM4EU QA/QC program but deemed comparable; c) biomarker data generated before HBM4EU QA/QC program but not deemed comparable.

In Table 2 urinary concentrations of different As species are shown. What is noticed immediately, is that results of recent As analysis are still heterogenous. As explained above not all studies have information on all As species. HBM4EU took a step forward in aligning the design and

Table 1
Overview of considered exposure determinants based on individual characteristics, geographical information and data retrieved from questionnaires per study.

Variable	Study					
	BEA (Spain)	Riksmaten adolescents (Sweden)	GerES V-sub (Germany)	SLO CRP (Slovenia)	FLEHS IV (Belgium)	ESTEBAN (France)
Sex (F/M)	x	x	x	x	x	x
BMI	x	x	x	x	x	x
NUTS region	x	x	x		x	x
Degree of urbanization	x	x	x	x	x	x
Sampling month	x	x	x	x	x	x
Sampling season	x	x	x	All same category	x	x
Frequency consumption of seafood	x	x	x	x	x	x
Frequency consumption of fish food	x	x	x	x	x	x
Frequency consumption of shellfish		x	x	x	x	x
Frequency consumption of meat	x		x	x	x	x
Frequency consumption of organ meat			x	x	x	x
Frequency consumption of poultry			x	x		x
Frequency consumption of milk	x		x	x	x	x
Frequency consumption of eggs			x	x	x	x
Vegetarian (no/yes)		x	x	All same category (no vegetarians)		x
Frequency consumption of vegetables		x	x	x	x	x
Frequency consumption of fruit		x	x	x	x	x
Frequency consumption of bread		x	x	x	x	x
Frequency consumption of cereals			x	x	x	x
Frequency consumption of rice			x	x		x
Recent consumption of rice (3 days before sampling)		x[a]		x	x	
Recent consumption of seafood (3 days before sampling)		x[a]	x	x	x	x
Frequency consumption of juices/sugar drinks			x	x		x
Frequency consumption of local food				x	x	
Frequency consumption of tea/coffee			x	x		x
Using vitamin B supplements (no/yes)				x		
Using folic acid supplements (no/yes)						
Using sea food supplements (no/yes)						
Use of pesticides indoor (no/yes)			x	x	x	x
Type of drinking water (bottled, tap, ground, other)	x			x		x
Tap water source at home (public, private, both public & private)	x	x	All same category	x	x	
Living close to waste incinerator (no/yes/do not know)	x			x		x
Smoking (no/yes)	x	x	x	All same category	x	x
Passive smoking (no/yes)	x		x	x	x	x
Use of alcohol (no/yes)	x	x	x	x	x	
ISCED	x	x	x	x	x	x
Income	x			x	x	x

An x means that data were available.
Data were not always uniformly distributed over different categories of the variables. For some categories the number of participants was small. Therefore in the statistical analysis categories were sometimes combined.
NUTS: https://ec.europa.eu/eurostat/web/nuts/background.
Degree of urbanization: DEGURBA: cities/towns and suburbs/rural areas (Dijkstra, 2014).
ISCED: International Standard Classification of Education, highest education in the household.
Income: equivalent household income.
The food frequency questions had six options according to individual frequency consumption of each item in the prior four weeks: Never, Rarely: <1 time/month, Sometimes: ≤ 1 time/week but ≥ 1 time/month, Often: 2–3 times/week, Very Often: 4–6 times/week, Everyday: ≥ 7 times/week.
[a] Based on registered consumption the day before urine sampling (and not on 3 days).

conduct of national and regional HBM surveys, but more effort is needed to further improve harmonization of As analysis across European studies. The Horizon Europe PARC project (PARC: Partnership on the Assessment of Risks of Chemicals) aims to increase upfront harmonization of HBM study designs (including exposure biomarkers), protocols and questionnaires.

For total arsenic, it is clear that the studies of Riksmaten adolescents (Sweden) and BEA (Spain) have a significantly higher geometric mean As_{tot} concentration (or As(III)+As(V)+MMA + DMA + AB) compared to the studies of FLEHSIV (Belgium) and CRP (Slovenia). This is indicated in Table 2 by the different letters between brackets, showing the result of a Tukey analysis. Total arsenic measured in ESTEBAN was not compared in this analysis as results were generated before HBM4EU and found to be not deemed comparable. For Germany no values were available for total arsenic in HBM4EU. An earlier study described in literature reported for Germany a P50 of 4.5 μg/L and a P95 of 14 μg/L for total arsenic in children of GerES IV (Schulz et al., 2009). This is at the lower part of current findings in other EU countries in HBM4EU, however, as the study was not part of HBM4EU, an exact comparison can't be made.

When focusing on toxic relevant arsenic, absolute GM values of TRA in HBM4EU varied between 3.84 and 8.47 μg/L (normalized for SG; see Table 2). Previous studies in literature reported for TRA a GM of 4.8 μg/L in adolescents of FLEHSII (Schoeters et al., 2012), a median of 4.54 μg/L in children and adolescents of GerES IV (Becker et al., 2008), a GM of 4.26 μg/L in children of Italy (Bocca et al., 2020) and a GM of 2.17 μg/L in children of the CROME-LIFE + study, Slovenia (Stajnko et al.,

Table 2
Speciated HBM urinary As concentrations (μg/L normalized for SG, except for ESTEBAN) in HBM4EU studies.

Study		As (III)	As(V)	MMA	DMA	AB	As_{tot}	As(III)+As (V)+MMA + DMA +AB	As(III)+ As(V) +MMA	TRA = As(III)+ As(V)+MMA + DMA	TRA/(As(III)+As (V)+MMA + DMA + AB)[a]	TRA/ As_{tot}[a]
FLEHS IV (Belgium; n=148)	GM	0.19 (A)[d]	NC	0.39 (A)[d]	3.46 (BC)[d]	1.25 (A)[d]	NA	9.24(A)	0.91(A)	4.52(A)	0.49	
	GSD	4.48		3.90	1.77	20.60		2.71	2.06	1.71		
GerES V-sub (Germany; n=300)	GM	0.28 (B)[d]	NC	NA	2.98 (AB)[d]	0.78 (A)[d]	NA	NA	NA	NA	NA	
	GSD	1.98			1.95	9.02						
Riksmaten adolescents (Sweden; n=300)	GM	0.31 (B)[c]	0.24 (A)[c]	1.48 (C)[c]	3.76 (C)[c]	9.59 (B)[c]	27.78 (B)[c]	22.29(B)	2.15(C)	6.20(B)	0.28	0.22
	GSD	1.74	1.95	1.60	1.93	7.28	3.06	3.14	1.43	1.60		
SLO CRP (Slovenia; n=97)	GM	0.32 (B)[d]	NC[e]	0.78 (B)[d]	2.48 (A)[d]	NA	7.94 (A)[d]	NA	1.22(B)	3.84(A)		0.48
	GSD	2.01		1.78	1.99		2.34		1.65	1.78		
BEA (Spain; n=300)	GM	0.45 (C)[c]	0.34 (B)[c]	1.31 (C)[c]	5.70 (D)[c]	10.73 (B)[c]	32.06 (B)[c]	25.42(B)	2.34(C)	8.47(C)	0.33	0.26
	GSD	2.04	2.50	1.82	2.08	6.49	2.97	3.08	1.62	1.79		
ESTEBAN[b] (France; n=300)	GM	NA	NA	NA	NA	NA	17.34[e]	NA	NA	5.48(B)		0.32
	GSD						2.51			1.80		

AB: arsenobetaine; MMA: methylarsonate acid; DMA: dimethylarsinate; As_{tot}: total arsenic; TRA: toxic relevant arsenic, i.e. As(III)+As(V)+MMA + DMA.
All data of different quality assured/quality controlled categories were included for this table and further analysis (Gilles et al., 2021).
GerES V-sub is an unweighted subset of the nationally representative GerES V.
GM: geometric mean; GSD: geometric Standard Deviation.
All concentrations were normalized for specific gravity (SG) except for ESTEBAN for which SG was not available.
NA: Not Available.
NC: Not Calculated. For AsV in FLEHS IV, CRP and GerES V-sub no GM was calculated as the detection frequency was less dan 60%. LOD and LOQ values are given in the supplementary material (Table A1).
Different letters between brackets point to significant differences between studies by a Tukey test (p at 0.05). No adjustments for influencing factors as age, sex, sampling year were done.
[a] Based on geomean values.
[b] TRA is available as a measured sum of species in ESTEBAN. No data on individual species was made available. For all other studies analysed species were summed to calculate TRA.
[c] Biomarker data quality assured by HBM4EU QA/QC program (Esteban López et al., 2021).
[d] Biomarker data generated before HBM4EU QA/QC program but deemed comparable.
[e] Biomarker data generated before HBM4EU QA/QC program but not deemed comparable.

2019). These values are all in the same order of magnitude as those observed in the HBM4EU Aligned Studies but comparability is hampered as these studies did not participate in the HBM4EU QA/QC.

The total urinary As concentration may be higher in some countries compared to others but this does not mean that the share of toxic arsenic is higher. When the contribution of TRA to As_{tot} or to the sum of As(III), As(V), MMA, DMA and AB is studied, it is shown that two HBM4EU studies reported a relatively larger contribution of TRA. Based on the geomeans following ratios were calculated: 0.22 to 0.33 for Riksmaten adolescents, BEA and ESTEBAN while for FLEHSIV and CRP this ratio varied between 0.48 and 0.49 (see Table 2). This means relatively to the total measured arsenic, more urinary toxic relevant arsenic is observed in Belgium and Slovenia.

Next, correlations between different As species were studied. Table 3 shows Pearson correlation coefficients between the As species based on non-imputed ln-transformed data for all studies combined. In human urine, all measured As species are significantly correlated, with the weakest significant correlation for As(V) and MMA (Pearson coefficient 0.103; p-value = 0.014). Associations between different As species are graphically displayed in the supplementary material in Figure A1. The highest Pearson correlation coefficient observed with TRA was for DMA (coefficient equal to 0.943; p-value = 0.001). DMA is quantitatively the major constituent of TRA as can be seen from Table 2. DMA is not a perfect marker for the intake of toxic inorganic arsenic. It originates from the intake of iAs but there are indications for direct intake and intake through arsenosugars and -lipids. It has already been shown that arsenobetaine is a main marker for the intake of seafood and that DMA co-occurs with arsenobetaine (Navas-Acien et al., 2011). HBM4EU data show that larger DMA concentrations are found with larger arsenobetaine concentrations (Table 3). Also Navarro Serrano et al. (2016) reported in their analysis a connection between urinary DMA and urinary arsenobetaine, indicating that the estimated risk when using As (III)+As(V)+MMA + DMA as a marker for exposure to iAs could be misleading (Navarro Serrano et al., 2016). The association clearly shows that a fraction of DMA is probably linked to similar sources as arsenobetaine. Therefore the suggestion is made to also measure As species as DMA in food items to get a clearer view of how much DMA originates from the intake of iAs and how much comes from other As sources (Carlin et al., 2016). It could be useful to calculate the contribution of directly ingested DMA because this could be used to subtract such DMA from urinary DMA levels for estimation of exposure to inorganic arsenic, as DMA(V) is less toxic than iAs (Hughes, 2002). The contribution of arsenosugars and -lipids should be explored as well. Another option could be to normalize TRA for the intake of arsenobetaine when a comparison would be made with a guidance value for toxicity for iAs. In doing so, one could take into account DMA associated with the intake of arsenobetaine as a marker for the intake of organic arsenic. However this would only solve partly the problem because there is also DMA coming from rice for example, not associated with AB (Guillod-Magnin et al., 2018) (Šlejkovec et al., 2021) (EFSA, 2021).

3.2. Exposure determinants

In the current study, we used questionnaire information filled out by the teenagers to associate information on food intake with their individual HBM data and this for a large dataset (see Table A2 in the

Table 3
Pearson correlation analysis between different As species (sg normalized and ln transformed).

		As(V)	MMA	DMA	AB	As_{tot}	As(III)+As(V)+MMA + DMA + AB	As(III)+As(V)+ MMA	TRA = As(III)+As(V)+ MMA + DMA
As(III)	N	677	764	1037	881	666	681	768	768
	Pearson coefficient	0.356	0.157	0.462	0.168	0.219	0.222	0.510	0.525
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
As(V)	N		572	711	683	531	572	572	572
	Pearson coefficient		0.103	0.391	0.194	0.213	0.231	0.547	0.498
	p-value		0.014	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
MMA	N			812	691	691	721	812	812
	Pearson coefficient			0.220	0.118	0.195	0.226	0.854	0.426
	p-value			<0.001	0.002	<0.001	<0.001	<0.001	<0.001
DMA	N				957	696	748	844	844
	Pearson coefficient				0.447	0.619	0.601	0.418	0.943
	p-value				<0.001	<0.001	<0.001	<0.001	0.001
AB	N					592	713	713	713
	Pearson coefficient					0.925	0.931	0.154	0.411
	p-value					<0.001	0.001	<0.001	<0.001
Astot	N						600	696	696
	Pearson coefficient						0.997	0.355	0.635
	p-value						<0.001	<0.001	<0.001
As(III)+As(V)+MMA + DMA + AB	N							748	748
	Pearson coefficient							0.329	0.623
	p-value							<0.001	<0.001
As(III)+As(V)+MMA	N								844
	Pearson coefficient								0.656
	p-value								<0.001

Not imputed values were used; Data below LOQ not included.
Data of ESTEBAN were not included as no sg normalized values were available.

supplementary material for detailed information on questionnaire answers). Multiple linear regression analysis showed that the sum of As (III), As(V), MMA, and DMA was significantly associated with (recent) seafood and/or rice consumption in all cohorts ($p < 0.05$) and not significantly with other food types (see Table 4). It is shown in Table 1 which food types were questioned in which study. It also can be seen from Table 1 that there are many gaps in the questionnaire data so more harmonization is needed in advance. Regarding As from drinking water, in the HBM4EU Aligned Studies, the distribution of participants across different categories of use of drinking water was not uniform and often there was a limited amount of participants in some categories (e.g. use of groundwater as drinking water). Studies in HBM4EU were not performed in areas with highly contaminated soil and groundwater. For smoking and alcohol, no significant association was detected in the multiple regression analysis of the current HBM4EU studies, however few adolescents reported smoking.

No significant associations were found with studied food types excluding rice and seafood. However literature data on As levels in food show that the main sources of exposure to iAs in European adolescents and adults are rice, grains and grain-based products, drinking water, and to a lesser extent vegetables, fruits, and seafood (Cubadda et al., 2016; Mania et al., 2017; González et al., 2019; Menon et al., 2020; EFSA, 2021). Some seaweed and mushroom types, dietary supplements based on seaweed and algae, and green teas can have a high iAs content, but since consumption is relatively limited in the average population, their contribution to total iAs exposure is generally small (EFSA, 2014; Mania et al., 2014; Braeuer and Goessler, 2019; EFSA, 2021). Nevertheless, a Danish study concluded that dietary supplements based on herbs, other botanicals, and algae may contribute to iAs exposure considerably (Hedegaard et al., 2013). Also, Cheyns et al. (2021) reported that food supplements based on algae or cyanobacteria may pose a health risk due to elevated concentrations of arsenic species.

Literature data on HBM show that associations of the sum As(III), As (V), MMA, and DMA measured in urine with consumption of seafood were also reported in adult populations in France, Italy and Slovenia (Fillol et al., 2010) (Saoudi et al., 2012) (Vimercati et al., 2017) (Minichilli et al., 2018) (Snoj Tratnik et al., 2019). Associations were also found with wine and beer consumption in France and Italy, hypothesized to be related to pesticide use (Fillol et al., 2010) (Saoudi et al., 2012) (Minichilli et al., 2018). In children living near agricultural sites in Spain, increased arsenic concentrations were found in hair (Molina-Villalba et al., 2015). Vimercati et al. (2017) did however not find an association between the sum of urinary As(III), As(V), MMA and DMA and the use of pesticides. Nowadays, the application of arsenic containing pesticides is not allowed in the EU. In areas affected by natural or anthropogenic arsenic contamination in Italy, Hungary, Slovakia, Romania, and the UK, correlations of the sum of As(III), As(V), MMA and DMA with tap, spring or well water consumption were found (Lindberg et al., 2006) (Middleton et al., 2016) (Vimercati et al., 2017) (Minichilli et al., 2018). A number of studies reported (weak) associations of urinary sum TRA with smoking (Lindberg et al., 2006) (Vimercati et al., 2017) (Minichilli et al., 2018). It should be noted that of all studies cited above, only one (Fillol et al., 2010) included teenagers (48 participants between 7 and 18 years of age); an association of As(III)+As(V)+MMA + DMA levels with age was however in general not identified. Saoudi et al. (2012) did find a positive association with age until the age of 55. Associations with sex are not that clear. Some studies show lower concentrations in women while in others it's the other way around (Fillol et al., 2010) (Vimercati et al., 2017). In some studies findings with sex may also be related to BMI, in case there is no correction for BMI. There may be an association between BMI and As with As being a possible causal contributor to obesity (Eick and Steinmaus, 2020). Also women in

Table 4
Final backward multiple linear regression analysis for ln TRA.

Study	Variable	Overall p value	Categories	N	Beta	95%CI		Pairwise p value
						LL	UL	
Riksmaten adolescents	Intercept	0.039			9.08	0.46	17.70	
	SG	0.108			−6.91	−15.35	1.53	
	Recent rice consumption	**0.006**	No	206	−0.16	−0.27	−0.04	0.006
			Yes	94	Reference = 0			
	Recent seafood consumption	**0.006**	No	203	−0.16	−0.27	−0.05	0.006
			Yes	97	Reference = 0			
	Highest ISCED household	**0.013**	ISCED 0-2	23	0.10	0.09	0.49	0.004
			ISCED 3-4	103	0.06	−0.12	0.10	0.870
			ISCED ≥5	174	Reference = 0			
	Model	**<0.001**						
FLEHS IV	Intercept	0.477			−5.80	−21.90	10.30	
	SG	0.322			7.85	−7.79	23.50	
	BMI	**0.008**			−0.04	−0.07	−0.01	
	Sex	**0.052**	Female	60	0.20	−0.01	0.41	0.052
			Male	51	Reference = 0			
	Recent rice consumption	**0.014**	No	76	−0.28	−0.50	−0.06	0.014
			Yes	35	Reference = 0			
	NUTS2 regions	**0.018**						
	Model	**<0.001**						
SLO CRP	Intercept	0.895			1.72	−14.12	17.57	
	SG	0.955			0.44	−15.07	15.95	
	Matrix (sampling method)	0.996	Morning urine	81	0.01	−0.28	0.28	0.996
			Spot urine	15	Reference = 0			
	Sampling month	**0.005**	January	40	−0.32	−0.56	−0.06	0.013
			February	27	−0.44	−0.72	−0.16	0.002
			March	29	Reference = 0			
	Seafood consumption	**0.002**	Never	43	−0.43	−0.67	−0.18	<0.001
			Rarely (<1 time/month)	22	−0.14	−0.43	0.14	0.327
			Sometimes (≤ 1 time/week but ≥ 1 time/month)	31	Reference = 0			
	Recent consumption seafood	**<0.001**	No	74	−0.45	−0.70	−0.19	<0.001
			Yes	22	Reference = 0			
	Model	**<0.001**						
BEA	Intercept	0.293			6.39	−4.99	17.78	
	SG	0.483			−3.97	−15.10	7.16	
	Matrix (sampling method)	0.719	Morning urine	197	−0.03	−0.19	0.13	0.719
			Spot urine	72	Reference = 0			
	Seafood consumption	**0.022**	Never	11	−0.46	−0.92	−0.01	0.049
			Rarely (<1 time/month)	8	−0.79	−1.30	−0.28	0.003
			Sometimes (≤ 1 time/week but ≥ 1 time/month)	39	−0.20	−0.56	0.14	0.252
			Often (2–3 times/week)	99	−0.18	−0.51	0.14	0.262
			Very Often (4–6 times/week)	97	−0.12	−0.44	0.20	0.460
			Everyday (≥ 7 times/week)	15	Reference = 0			
	Model	**<0.001**						
ESTEBAN	Intercept	<0.001						
	Recent consumption of seafood	**<0.001**	No	157	−0.46	−0.67	−0.24	<0.001
			Yes	37	Reference = 0			
	NUTS3 regions	**0.005**						
	Model	**<0.001**						

ISCED: International Standard Classification of Education: Low education (ISCED 0–2), Medium education (ISCED 3–4), High education (ISCED ≥ 5).
NUTS: Nomenclature Of Territorial Units for Statistics.
CI: Confidence Interval; LL: lower limit; UL: upper limit.
SG and matrix (first morning urine; spot urine) forced into the model except for ESTEBAN.
All biomarker data (μg/L) were normalized for specific gravity (SG) except for ESTEBAN for which SG was not available.
Only those variables with $p < 0.05$ were kept in the multiple regression analysis.
Beta is the value by which ln TRA changes. The actual change of TRA equals exp (beta).
For GerES V-sub no data on TRA were available.

childbearing age may have a higher As methylation efficiency (Lindberg et al., 2008).

Table 5 presents the multiple linear regression analysis for the sum of As(III), As(V), MMA and DMA with arsenobetaine taken up in the model as a co-variate. In the study of Riksmaten adolescents the consumption of seafood, dropped both out of the model as significant exposure determinant ($p > 0.05$) (Table 5). Considering food, only recent rice consumption remained in the model. For the FLEHS IV study, also only recent rice consumption remained in the model possibly overshadowing other determinants. In the BEA study no significant variables associated with food consumption were observed. This could be related by a lack of information on drinking water concentrations and on consumption of specific food types high in iAs (dietary supplements, seaweed, mushrooms). This information is not available (see Table 1). In the Riksmaten adolescents cohort, a significant effect of sampling season was found, with lower observed concentration of TRA in summer.

Another reason why few significant association with food items were observed in the HBM4EU studies can be that besides consumption of certain food types associated with higher iAs exposure, food types decreasing As exposure takes place as well. In the US, higher consumption of milk and milk products, vegetables, organ and other meats, and nutritional drinks was found to be associated with lower concentrations of organic as well as inorganic arsenic. It will be of interest to investigate possible interactions/mechanisms responsible for lower excretion of As when certain foods like milk and milk products, vegetables, and organ meats are consumed (Jain, 2021). Associations may reflect nutrients found in certain foods associated with As metabolism such as Zn and Fe, Se, vit B12, etc. (Steinmaus et al., 2005; Krohn et al., 2016; Howe et al., 2017).

3.3. Toxicity and comparison with HBM guidance values (non-) carcinogenic effects

A causal association between human arsenic exposure and lung, skin,

Table 5
Final backward multiple linear regression analysis for ln TRA with arsenobetaine in model.

Study	Variable	Overall p value	Categories	N	Beta	95%CI		Pairwise p value
						LL	UL	
Riksmaten adolescents	Intercept	0.071			7.79	−0.63	16.21	
	Arsenobetaine	<0.001			0.09	0.06	0.11	
	SG	0.172			−5.71	−13.93	2.51	
	Sampling season	**0.051**	Spring	70	−0.05	−0.19	0.09	0.538
			Summer	25	−0.25	−0.44	−0.05	0.013
			Autumn	100	0.01	−0.12	0.14	0.828
			Winter	74	Reference = 0			
	Recent rice consumption	**0.020**	No	188	−0.13	−0.25	−0.02	0.020
			Yes	81	Reference = 0			
	Highest ISCED household	**0.044**	ISCED 0-2	22	0.25	0.05	0.44	0.013
			ISCED 3-4	93	0.03	−0.07	0.15	0.545
			ISCED ≥5	154	Reference			
	Model	**<0.001**						
FLEHS IV	Intercept	0.825			−1.55	−13.55	10.45	
	Arsenobetaine	**0.002**			0.04	0.02	0.07	
	SG	0.541			3.63	−8.08	15.34	
	BMI	**0.013**			−0.03	−0.05	−0.01	
	Recent rice consumption	**<0.001**	No	97	−0.31	−0.48	−0.14	<0.001
			Yes	51	Reference = 0			
	NUTS2 regions	**<0.001**						
	Model	**<0.001**						
BEA	Intercept	0.110			7.92	−1.51	17.36	
	Arsenobetaine	**<0.001**			0.15	0.11	0.18	
	SG	0.217			−5.81	−15.06	3.43	
	Matrix (sampling method)	0.865	Morning urine	197	−0.01	−0.14	0.12	0.865
			Spot urine	74	Reference = 0			
	NUTS1 regions	**0.015**						
	Model	**<0.001**						

NUTS: Nomenclature Of Territorial Units for Statistics.
CI: Confidence Interval; LL: lower limit; UL: upper limit.
SG and matrix (first morning urine; spot urine) forced into the model.
All datasets were normalized for specific gravity (SG).
Beta is the value by which ln (As(III)+As(V)+MMA + DMA) changes. The actual change of As(III)+As(V)+MMA + DMA equals exp (beta).
Only those variables with $p < 0.05$ were kept in the multiple regression analysis.
For SLO CRP and ESTEBAN no data on arsenobetaine was available and for GerES V-sub no data on TRA.

and bladder cancer has been recognized at high exposure (NRC, 2013; USEPA, 2019). 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 relatively robust. Causal associations with liver and kidney cancer, non-malignant respiratory disease, neurodevelopment, and effects on the immune system are less certain according to US EPA (NRC, 2013) (USEPA, 2019). US EPA is currently performing an in depth investigation of the shape of the dose-response curves in the low dose region.

In 2010 Hays et al. derived guidance values for TRA in urine (Hays et al., 2010). For non-cancer effects the BE (Biomonitoring Equivalent) value was equal to 6.4 μg/L or 8.3 μg/g creatinine (persons >6y). The point of departure (POD) is 0.8 μg/kg BW/day (USEPA: https://iris.epa.gov/static/pdfs/0278_summary.pdf) which originates from a human study (hyperpigmentation and vascular complications). Assuming steady state conditions an internal urinary concentration of 19.3 μg/L was estimated. By applying an assessment factor of 3 for intrahuman differences a value of 6.4 μg/L was obtained. This corresponds US EPA's Reference Dose and the Agency for Toxic Substances and Disease Registry's Minimal Risk Level of 0.3 μg/kg bw/day. Above this value, health effects cannot be excluded. This value needs an update as new information on toxicity of arsenic is available and epigenetic changes are reported (Kenyon, 2021; Chakraborty et al., 2022). In addition, as pointed out by Hays et al. (2010), this BE value does not consider carcinogenicity of arsenic. For the Canadian Health Measures Survey (CHMS) St-Amand et al. (2014) set the BE value for the sum of MMA and DMA at 5.8 μg/L. This was done because of detection problems of arsenite and arsenate (Aylward et al., 2013; St-Amand et al., 2014). In France, INRS stated that the reference value in the general population of As(III)+As(V)+MMA + DMA should be lower than 10 μg/L or 10 μg/g creatinine and As(III)+As(V) should be lower than 2.2 μg/L (Fillol et al., 2010). So a dual guidance value was set.

Studies included here (Fig. 1) show that P50 value was lower than the BE-value of 6.4 μg/L except in the dataset of Spain (BEA). P95 values all exceeded the BE value. In the BEA study the P95 value equaled 21.5 μg/L. The percentage of teenagers exceeding the BE-value varied between 16 and 52%: SLO CRP 16%, FLEHS IV 22%, Riksmaten adolescents 38%, ESTEBAN 39% and BEA 52%. No data on MMA were available for GerES V-sub which means that TRA could not be calculated. Values higher than the BE value are an indication for policymakers and risk managers and pinpoint the need to have a closer look at the risk assessment. It is an indication for a reason of concern, certainly for highly exposed individuals or vulnerable populations. To reduce exposure in children, it is for example recommended that products based on rice (rice waffles) are not consumed by children on a regular basis (BFR, 2014). This is supported by the Health Council in Belgium (Hoge Gezondheidsraad, 2018).

Inorganic arsenic is a carcinogen. There is uncertainty related to the dose-response relation of arsenic-induced cancers at low exposure levels; although there is mechanistic evidence suggesting a potential threshold for its carcinogenicity (Snow et al., 2005; Yager et al., 2013), the data have been usually considered insufficient for the identification of such thresholds and a linear approach for the cancer risk assessment has been used as a default. Risk specific doses (RSD) have been calculated for a range of risk levels of interest from $1x10^{-4}$ to $1x10^{-6}$ (i.e. BE_{RSD} or biomonitoring equivalents at the RSD). They provide an estimate of the steady-state concentrations that would result from chronic exposure, over a lifetime at the RSD (Aylward et al., 2013). The BE_{RSD} value corresponding to an extra cancer risk of $1x10^{-6}$ equals 0.0065 μg TRA/L (Sean M. Hays et al., 2010), based on a cancer slope derived by USEPA for a study on lung and bladder cancer among a Taiwanese population exposed via drinking water (Morales et al., 2000). Cancer risks for the HBM4EU Aligned Studies corresponding to the 50th exposure percentile were estimated assuming linear extrapolation. Extra lifetime cancer risks equaled $5.7x10^{-4}$ to $1.0x10^{-3}$ depending on the study. However, discussions on the existence of a threshold for lung- and bladder cancers continue (Tsuji et al., 2021). Other assumptions used in the assessment include linearity of the dose-response relation, lifetime exposure, constant bodyweight, satisfactory nutritional status and no changes in metabolism. The calculated values must be interpreted with caution, particularly as the development of an updated assessment of toxicity of iAs, including the shape of dose-response curves in the low dose region, is ongoing by USEPA (NASEM, 2019).

The study addresses exposure, exposure determinants and risk of arsenic in adolescents of the general population. Strengths are the homogenization of protocols under HBM4EU and the QA/QC so that

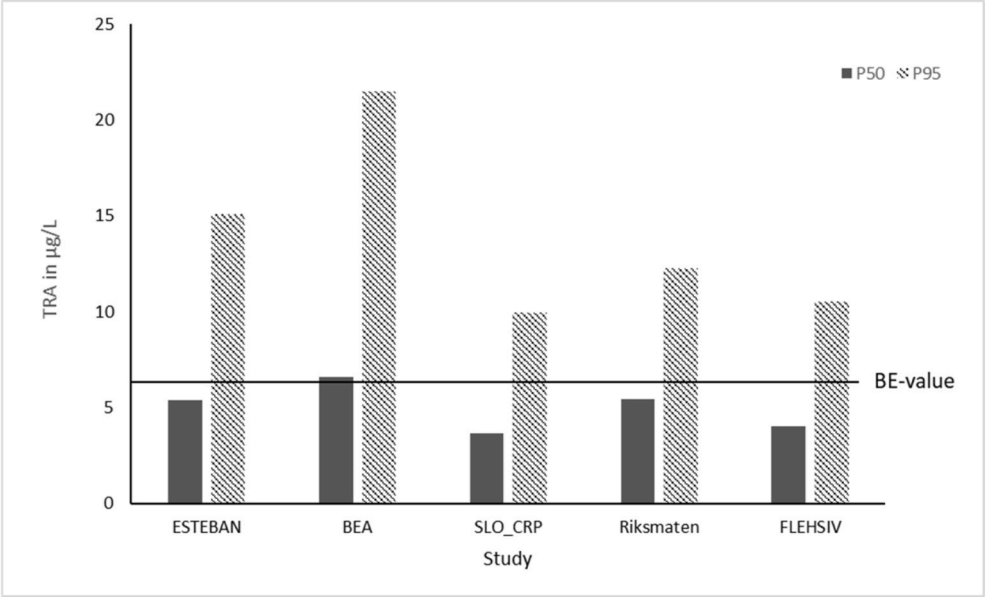

Fig. 1. Comparison of 50th percentile (P50) and 95th percentile (P95) arsenic concentrations (TRA) with HBM guidance value by Hays et al., (2010) (BE-value: 6.4 μg/L based on non-carcinogenic effects). Values in this figure were not normalized by SG. Riksmaten = Riksmaten adolescents. GerES V-sub is not presented as TRA was not determined.

harmonized results for exposure and questionnaire data can be obtained if taken into account *a priori*. The study covered the different EU regions (North, South, East, West) and by selection adolescents it is focusing on a vulnerable population for which the possibility exists that later in life resampling may take place. Some limitations are that not all As species were measured and that also in the questionnaires some information was missing. Therefore questionnaire were developed within HBM4EU to use in future studies.

4. Conclusion

HBM4EU made a big step in collecting comparable HBM data creating the largest dataset representing As exposure of adolescents living in Europe. Nevertheless, analysis of different As species needs more harmonization in the EU in future campaigns as results of recent analysis are still too heterogeneous. Also future questionnaire data with specific questions on arsenic exposure determinants (e.g. consumption of food supplements, seaweed, selenium status, smoking status) need more harmonization in advance. This will allow a combination of datasets which will increase statistical power. Besides, when addressing certain research questions on the source or determinant of exposure, more attention can go to selection of participants as not each study is *a priori* designed to answer all the questions for a certain chemical. Toxicologically relevant arsenic concentrations (TRA) varied a factor 2 between studies. The P95 exceeded the current biomonitoring equivalent (BE) of 6.4 μg/L for non-cancer effects in each study, and cancer risks related to arsenic exposure cannot be neglected although there is a lot of uncertainty at low dose exposure. Exposure determinants pointed in the direction of rice and seafood as main exposure determinants for TRA which overshadow the role of others. After adjusting for seafood intake, only rice intake remained significant. More HBM data (additional age groups, wider geographical spread) are needed related to arsenic exposure through groundwater consumption/use, co-exposure with other pollutants, and for vulnerable populations including information on ethnicity, genetic polymorphism and epigenetics. By combining HBM4EU studies, the statistical power increased and significant associations between all studied arsenic species appeared with some strong and some weak associations. A strong association was found between DMA and arsenobetaine. DMA may originate from inorganic arsenic but also from the direct intake of food or from the intake of organoarsenicals. Therefore, to properly identify human iAs exposure and to reduce iAs exposure efficiently in vulnerable populations, more information on the contribution of direct intake of DMA from food could be obtained which can be subtracted from urinary DMA concentrations. The role of arsenosugars and arsenolipids as sources of urinary DMA should be explored as well.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2023.114115.

References

Andrewes, P., Demarini, D.M., Funasaka, K., Wallace, K., Lai, V.W.M., Sun, H., Cullen, W. R., Kitchin, K.T., 2004. Do arsenosugars pose a risk to human health? The comparative toxicities of a trivalent and pentavalent arsenosugar. Environ. Sci. Technol. 38, 4140–4148. https://doi.org/10.1021/ES035440F.

Aylward, L.L., Kirman, C.R., Schoeny, R., Portier, C.J., Hays, S.M., 2013. Evaluation of biomonitoring data from the CDC national exposure report in a risk assessment context: perspectives across chemicals. Environ. Health Perspect. 121, 287–294. https://doi.org/10.1289/ehp.1205740.

Becker, K., Müssig-Zufika, M., Conrad, A., Lüdecke, A., Schulz, C., Seiwert, M., Kolossa-Gehring, M., 2008. German Environmental Survey for Children 2003/06 - GerES IV-Human Biomonitoring - Levels of Selected Substances in Blood and Urine of Children in Germany.

BFR, 2014. Arsenic in Rice and Rice Products.

Bocca, B., Pino, A., Brumatti, L.V., Rosolen, V., Ronfani, L., D'Aversa, J., Ruggieri, F., Petrucci, F., Calamandrei, G., Barbone, F., Alimonti, A., 2020. Children exposure to inorganic and organic arsenic metabolites: a cohort study in Northeast Italy. Environ. Pollut. 265 https://doi.org/10.1016/J.ENVPOL.2020.114826.

Braeuer, S., Goessler, W., 2019. Arsenic species in mushrooms, with a focus on analytical methods for their determination - a critical review. Anal. Chim. Acta 1073, 1–21. https://doi.org/10.1016/J.ACA.2019.04.004.

Carlin, D.J., Naujokas, M.F., Bradham, K.D., Cowden, J., Heacock, M., Henry, H.F., Lee, J.S., Thomas, D.J., Thompson, C., Tokar, E.J., Waalkes, M.P., Birnbaum, L.S., Suk, W.A., 2016. Arsenic and environmental health: state of the science and future research opportunities. Environ. Health Perspect. 124, 890–899. https://doi.org/10.1289/ehp.1510209.

Chakraborty, A., Ghosh, S., Biswas, B., Pramanik, S., Nriagu, J., Bhowmick, S., 2022. Epigenetic modifications from arsenic exposure: a comprehensive review. Sci. Total Environ. 810 https://doi.org/10.1016/J.SCITOTENV.2021.151218.

Chen, J., Garbinski, L.D., Rosen, B., Zhang, J., Xiang, P., Ma, L.Q., 2019. Organoarsenical compounds: occurrence, toxicology and biotransformation, 217–243. https://doi.org/10.1080/10643389.2019.1619375 50. https://doi.org/10.1080/10643389.2019.1619375.

Cheyns, K., Demaegdt, H., Waegeneers, N., Ruttens, A., 2021. Intake of food supplements based on algae or cyanobacteria may pose a health risk due to elevated concentrations of arsenic species. Food Addit. Contam. Part A. Chem. Anal. Control. Expo. Risk Assess. 38, 609–621. https://doi.org/10.1080/19440049.2021.1877834.

Cubadda, F., D'Amato, M., Aureli, F., Raggi, A., Mantovani, A., 2016. Dietary exposure of the Italian population to inorganic arsenic: the 2012-2014 Total Diet Study. Food Chem. Toxicol. 98, 148–158. https://doi.org/10.1016/J.FCT.2016.10.015.

Dijkstra, L., 2014. A harmonised definition of cities and rural areas: the new degree of urbanisation. Eur. Comm. Dir. Reg. Urban Policy (DG REGIO) - Work. Pap.

Drobna, Z., Styblo, M., Thomas, D.J., 2009. An Overview of Arsenic Metabolism and Toxicity. Curr. Protoc. Toxicol. 42, 4.31.1. https://doi.org/10.1002/0471140856.TX0431S42.

EFSA, 2014. Dietary exposure to inorganic arsenic in the European population. EFSA J. 12, 3597.

EFSA, 2021. Chronic Dietary Exposure to Inorganic Arsenic.

Eick, S.M., Steinmaus, C., 2020. Arsenic and obesity: a review of causation and interaction. Curr. Environ. Heal. reports 7, 343–351. https://doi.org/10.1007/S40572-020-00288-Z.

Esteban López, M., Göen, T., Mol, H., Nübler, S., Haji-Abbas-Zarrabi, K., Koch, H.M., Kasper-Sonnenberg, M., Dvorakova, D., Hajslova, J., Antignac, J.P., Vaccher, V., Elbers, I., Thomsen, C., Vorkamp, K., Pedraza – Díaz, S., Kolossa-Gehring, M., Castaño, A., 2021. The European human biomonitoring platform - design and implementation of a laboratory quality assurance/quality control (QA/QC) programme for selected priority chemicals. Int. J. Hyg Environ. Health 234. https://doi.org/10.1016/j.ijheh.2021.113740, 113740–113740.

Feldmann, J., Krupp, E.M., 2011. Critical review or scientific opinion paper: arsenosugars-a class of benign arsenic species or justification for developing partly speciated arsenic fractionation in foodstuffs? Anal. Bioanal. Chem. 399, 1735–1741. https://doi.org/10.1007/s00216-010-4303-6.

Fillol, C., Dor, F., Labat, L., Boltz, P., Le Bouard, J., Mantey, K., Mannschott, C., Puskarczyk, E., Viller, F., Momas, I., Seta, N., 2010. Urinary arsenic concentrations and speciation in residents living in an area with naturally contaminated soils. Sci. Total Environ. 408, 1190–1194. https://doi.org/10.1016/j.scitotenv.2009.11.046.

Francesconi, K.A., Tanggaard, R., McKenzie, C.J., Goessler, W., 2002. Arsenic metabolites in human urine after ingestion of an arsenosugar. Clin. Chem. 48, 92–101. https://doi.org/10.1093/CLINCHEM/48.1.92.

Ganzleben, C., Antignac, J.-P., Barouki, R., Castaño, A., Fiddicke, U., Klánová, J., Lebret, E., Olea, N., Sarigiannis, D., Schoeters, G.R., Sepai, O., Tolonen, H., Kolossa-Gehring, M., 2017. Human biomonitoring as a tool to support chemicals regulation in the European Union. Int. J. Hyg Environ. Health. https://doi.org/10.1016/j.ijheh.2017.01.007.

Gao, Y., Baisch, P., Mirlean, N., Rodrigues da Silva Júnior, F.M., Van Larebeke, N., Baeyens, W., Leermakers, M., 2018. Arsenic speciation in fish and shellfish from the North Sea (Southern bight) and Açu Port area (Brazil) and health risks related to seafood consumption. Chemosphere 191, 89–96. https://doi.org/10.1016/J.CHEMOSPHERE.2017.10.031.

Gezondheidsraad, Hoge, 2018. Arseen in voeding voor baby's en peuters.

Gilles, et al., 2022. Harmonisation of human biomonitoring studies in Europe: characteristics of the HBM4EU aligned studies participants - submitted. Environ. Res. Public Heal.

Gilles, L., Govarts, E., Rambaud, L., Vogel, N., Castaño, A., Esteban López, M., Rodriguez Martin, L., Koppen, G., Remy, S., Vrijheid, M., Montazeri, P., Birks, L., Sepai, O., Stewart, L., Fiddicke, U., Loots, I., Knudsen, L.E., Kolossa-Gehring, M., Schoeters, G., 2021. HBM4EU combines and harmonises human biomonitoring data across the EU, building on existing capacity - the HBM4EU survey. Int. J. Hyg Environ. Health 237. https://doi.org/10.1016/J.IJHEH.2021.113809.

González, N., Calderón, J., Rúbies, A., Timoner, I., Castell, V., Domingo, J.L., Nadal, M., 2019. Dietary intake of arsenic, cadmium, mercury and lead by the population of Catalonia, Spain: analysis of the temporal trend. Food Chem. Toxicol. 132 https://doi.org/10.1016/J.FCT.2019.110721.

González-Alzaga, B., Hernández, A.F., Kim Pack, L., Iavicoli, I., Tolonen, H., Santonen, T., Vinceti, M., Filippini, T., Moshammer, H., Probst- Hensch, N., Kolossa-Gehring, M., Lacasaña, M., 2022. The questionnaire design process in the European Human Biomonitoring Initiative (HBM4EU). Environ. Int. 160, 107071 https://doi.org/10.1016/J.ENVINT.2021.107071.

Guillod-Magnin, R., Brüschweiler, B.J., Aubert, R., Haldimann, M., 2018. Arsenic species in rice and rice-based products consumed by toddlers in Switzerland, 1164–1178. https://doi.org/10.1080/19440049.2018.1440641 35. https://doi.org/10.1080/19440049.2018.1440641.

Hays, Sean M., Aylward, L.L., Gagné, M., Nong, A., Krishnan, K., 2010. Biomonitoring equivalents for inorganic arsenic. Regul. Toxicol. Pharmacol. 58, 1–9. https://doi.org/10.1016/j.yrtph.2010.06.002.

Hedegaard, R.V., Rokkjær, I., Sloth, J.J., 2013. Total and inorganic arsenic in dietary supplements based on herbs, other botanicals and algae–a possible contributor to inorganic arsenic exposure. Anal. Bioanal. Chem. 405, 4429–4435. https://doi.org/10.1007/S00216-013-6835-Z.

Howe, C.G., Li, Z., Zens, M.S., Palys, T., Chen, Y., Channon, J.Y., Karagas, M.R., Farzan, S.F., 2017. Dietary B vitamin intake is associated with lower urinary monomethyl arsenic and oxidative stress marker 15-F2t-isoprostane among New Hampshire adults. J. Nutr. 147, 2289. https://doi.org/10.3945/JN.117.253419.

Hughes, M.F., 2002. Arsenic toxicity and potential mechanisms of action. Toxicol. Lett. 133, 1–16. https://doi.org/10.1016/S0378-4274(02)00084-X.

IARC, 2012. Arsenic, Metals, Fibres, and Dusts.

Jain, R.B., 2021. Contribution of diet and other factors for urinary concentrations of total arsenic and arsenic species: data for US children, adolescents, and adults. Environ. Sci. Pollut. Res. Int. 28, 50094–50116. https://doi.org/10.1007/S11356-021-14230-9.

Kenyon, E.M., 2021. Arsenic toxicokinetic modeling and risk analysis: progress, needs and applications. Toxicology 457, 152809. https://doi.org/10.1016/J.TOX.2021.152809.

Krishnakumar, P.K., Qurban, M.A., Stiboller, M., Nachman, K.E., Joydas, T.V., Manikandan, K.P., Mushir, S.A., Francesconi, K.A., 2016. Arsenic and arsenic species in shellfish and finfish from the western Arabian Gulf and consumer health risk assessment. Sci. Total Environ. 566 (567), 1235–1244. https://doi.org/10.1016/J.SCITOTENV.2016.05.180.

Krohn, R.M., Raqib, R., Akhtar, E., Vandenberg, A., Smits, J.E.G., 2016. A high-selenium lentil dietary intervention in Bangladesh to counteract arsenic toxicity: study protocol for a randomized controlled trial. Trials 17, 1–8. https://doi.org/10.1186/S13063-016-1344-Y/FIGURES/1.

Kuiper, J.R., O'Brien, K.M., Ferguson, K.K., Buckley, J.P., 2021. Urinary specific gravity measures in the U.S. population: implications for the adjustment of non-persistent chemical urinary biomarker data. Environ. Int. 156, 106656 https://doi.org/10.1016/J.ENVINT.2021.106656.

Lai, V.W.M., Sun, Y., Ting, E., Cullen, W.R., Reimer, K.J., 2004. Arsenic speciation in human urine: are we all the same? Toxicol. Appl. Pharmacol. https://doi.org/10.1016/j.taap.2003.10.033.

Lindberg, A.L., Goessler, W., Gurzau, E., Koppova, K., Rudnai, P., Kumar, R., Fletcher, T., Leonardi, G., Slotova, K., Gheorghiu, E., Vahter, M., 2006. Arsenic exposure in Hungary, Romania and Slovakia. J. Environ. Monit. 8, 203–208. https://doi.org/10.1039/b513206a.

Lindberg, A.L., Ekström, E.C., Nermell, B., Rahman, M., Lönnerdal, B., Persson, L.Å., Vahter, M., 2008. Gender and age differences in the metabolism of inorganic arsenic in a highly exposed population in Bangladesh. Environ. Res. 106, 110–120. https://doi.org/10.1016/J.ENVRES.2007.08.011.

Luvonga, C., Rimmer, C.A., Yu, L.L., Lee, S.B., 2020. Organoarsenicals in seafood: occurrence, dietary exposure, toxicity, and risk assessment considerations - a review. J. Agric. Food Chem. https://doi.org/10.1021/acs.jafc.9b07532.

Mania, M., Szynal, T., Rebeniak, M., Wojciechowska-Mazurek, M., Starska, K., Strzelecka, A., 2014. Human exposure asseessment to different arsenic species in tea. Rocz. Panstw. Zakl. Hig. 65, 281–286.

Mania, M., Rebeniak, M., Szynal, T., Starska, K., Wojciechowska-Mazurek, M., Postupolski, J., 2017. Exposure assessment of the population in Poland to the toxic effects of arsenic compounds present in rice and rice based products. Rocz. Panstw. Zakl. Hig. 68, 339–346.

Menon, M., Sarkar, B., Hufton, J., Reynolds, C., Reina, S.V., Young, S., 2020. Do arsenic levels in rice pose a health risk to the UK population? Ecotoxicol. Environ. Saf. 197 https://doi.org/10.1016/J.ECOENV.2020.110601.

Meyer, S., Matissek, M., Müller, S.M., Taleshi, M.S., Ebert, F., Francesconi, K.A., Schwerdtle, T., 2014. In vitro toxicological characterisation of three arsenic-containing hydrocarbons. Metallomics 6, 1023–1033. https://doi.org/10.1039/c4mt00061g.

Middleton, D.R.S., Watts, M.J., Hamilton, E.M., Ander, E.L., Close, R.M., Exley, K.S., Crabbe, H., Leonardi, G.S., Fletcher, T., Polya, D.A., 2016. Urinary arsenic profiles reveal exposures to inorganic arsenic from private drinking water supplies in Cornwall, UK. Sci. Rep. 6, 1–11. https://doi.org/10.1038/srep25656.

Minichilli, F., Bianchi, F., Maria Ronchi, A., Gorini, F., Bustaffa, E., 2018. Urinary arsenic in human samples from areas characterized by natural or anthropogenic pollution in Italy. Int. J. Environ. Res. Publ. Health 15. https://doi.org/10.3390/ijerph15020299.

Molina-Villalba, I., Lacasaña, M., Rodríguez-Barranco, M., Hernández, A.F., Gonzalez-Alzaga, B., Aguilar-Garduño, C., Gil, F., 2015. Biomonitoring of arsenic, cadmium, lead, manganese and mercury in urine and hair of children living near mining and industrial areas. Chemosphere 124, 83–91. https://doi.org/10.1016/J.CHEMOSPHERE.2014.11.016.

Morales, K.H., Ryan, L., Kuo, T.L., Wu, M.M., Chen, C.J., 2000. Risk of internal cancers from arsenic in drinking water. Environ. Health Perspect. 108, 655. https://doi.org/10.1289/EHP.00108655.

NASEM, 2019. Review of EPA's Updated Problem Formulation and Protocol for the Inorganic Arsenic IRIS Assessment.

Navarro Serrano, I., Llorente Ballesteros, M.T., Sánchez Fernández Pacheco, S., Izquierdo Álvarez, S., López Colón, J.L., 2016. Total and speciated urinary arsenic levels in the Spanish population. Sci. Total Environ. 571, 164–171. https://doi.org/10.1016/j.scitotenv.2016.07.134.

Navas-Acien, A., Francesconi, K.A., Silbergeld, E.K., Guallar, E., 2011. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. Environ. Res. 111, 110–118. https://doi.org/10.1016/j.envres.2010.10.009.

NRC, 2013. Critical aspects of EPA's IRIS assessment of inorganic arsenic. Interim Report.

R Core Team, 2018. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

Saoudi, A., Zeghnoun, A., Bidondo, M.L., Garnier, R., Cirimele, V., Persoons, R., Fréry, N., 2012. Urinary arsenic levels in the French adult population: the French national nutrition and health study, 2006-2007. Sci. Total Environ. 433, 206–215. https://doi.org/10.1016/j.scitotenv.2012.06.053.

Schmeisser, E., Goessler, W., Francesconi, K.A., 2006. Human metabolism of arsenolipids present in cod liver. Anal. Bioanal. Chem. 385, 367–376. https://doi.org/10.1007/S00216-006-0401-X.

Schoeters, G., Colles, A., Den Hond, E., Croes, K., Vrijens, J., Baeyens, W., Nelen, V., 2012. The Flemish Environment and Health Study (FLEHS) – second survey (2007-2011): establishing reference values for biomarkers of exposure in the Flemish population. In: Biomarkers and Human Biomonitoring. The Royal Society of Chemistry.

Schulz, C., Angerer, J., Ewers, U., Heudorf, U., Wilhelm, M., 2009. Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German environmental survey on children 2003-2006 (GerES IV). Int. J. Hyg Environ. Health 212, 637–647. https://doi.org/10.1016/J.IJHEH.2009.05.003.

Šlejkovec, Z., Gorše, L., Grobler, A., Jagodic, M., Falnoga, I., 2021. Arsenic speciation and elemental composition of rice samples from the Slovenian market. Food Chem. 342 https://doi.org/10.1016/J.FOODCHEM.2020.128348.

Snoj Tratnik, J., Falnoga, I., Mazej, D., Kocman, D., Fajon, V., Jagodic, M., Stajnko, A., Trdin, A., Šlejkovec, Z., Jeran, Z., Osredkar, J., Sešek-Briški, A., Krsnik, M., Kobal, A. B., Kononenko, L., Horvat, M., 2019. Results of the first national human biomonitoring in Slovenia: trace elements in men and lactating women, predictors of exposure and reference values. Int. J. Hyg Environ. Health 222, 563–582. https://doi.org/10.1016/J.IJHEH.2019.02.008.

Snow, E.T., Sykora, P., Durham, T.R., Klein, C.B., 2005. Arsenic, mode of action at biologically plausible low doses: what are the implications for low dose cancer risk? Toxicol. Appl. Pharmacol. 207, 557–564. https://doi.org/10.1016/J.TAAP.2005.01.048.

St-Amand, A., Werry, K., Aylward, L.L., Hays, S.M., Nong, A., 2014. Screening of population level biomonitoring data from the Canadian Health Measures Survey in a risk-based context. Toxicol. Lett. 231, 126–134. https://doi.org/10.1016/j.toxlet.2014.10.019.

Stajnko, A., Šlejkovec, Z., Mazej, D., France-Štiglic, A., Briški, A.S., Prpić, I., Špirić, Z., Horvat, M., Falnoga, I., 2019. Arsenic metabolites; selenium; and AS3MT, MTHFR, AQP4, AQP9, SELENOP, INMT, and MT2A polymorphisms in Croatian-Slovenian population from PHIME-CROME study. Environ. Res. 170, 301–319. https://doi.org/10.1016/j.envres.2018.11.045.

Steinmaus, C., Carrigan, K., Kalman, D., Atallah, R., Yuan, Y., Smith, A.H., 2005. Dietary intake and arsenic methylation in a U.S. population. Environ. Health Perspect. 113, 1153–1159. https://doi.org/10.1289/EHP.7907.

Tarvainen, T., Albanese, S., Birke, M., Poňavič, M., Reimann, C., Andersson, M., Arnoldussen, A., Baritz, R., Batista, M.J., Bel-Lan, A., Cicchella, D., Demetriades, A., De Vivo, B., Dinelli, E., De Vos, W., Duris, M., Dusza-Dobek, A., Eggen, O.A., Eklund, M., Ernstsen, V., Filzmoser, P., Finne, T.E., Flight, D., Forrester, S., Fuchs, M., Fugedi, U., Gilucis, A., Gosar, M., Gregorauskiene, V., Gulan, A., Halamić, J., Haslinger, E., Hayoz, P., Hobiger, G., Hoffmann, R., Hoogewerff, J., Hrvatovic, H., Husnjak, S., Janik, L., Johnson, C., Jordan, G., Kirby, J., Kivisilla, J., Klos, V., Krone, F., Kwecko, P., Kuti, L., Ladenberger, A., Lima, A., Locutura, J., Lucivjansky, P., Mackovych, D., Malyuk, B.I., Maquil, R., McLaughlin, M.J., Meuli, R. G., Miosic, N., Mol, G., Négrel, P., O'Connor, P., Oorts, K., Ottesen, R.T., Pasieczna, A., Petersell, V., Pfleiderer, S., Prazeres, C., Rauch, U., Salpeteur, Schedl, A., Scheib, A., Schoeters, I., Sefcik, P., Sellersjö, E., Skopljak, F., Slaninka, I., Šorša, A., Srvkota, R., Stafilov, T., Trendavilov, V., Valera, P., Verougstraete, V., Vidojević, D., Zissimos, A.M., Zomeni, Z., 2013. Arsenic in agricultural and grazing land soils of Europe. Appl. Geochem. 28, 2–10. https://doi.org/10.1016/j.apgeochem.2012.10.005.

Taylor, V., Goodale, B., Raab, A., Schwerdtle, T., Reimer, K., Conklin, S., Karagas, M.R., Francesconi, K.A., 2017. Human exposure to organic arsenic species from seafood. Sci. Total Environ. 580, 266–282. https://doi.org/10.1016/j.scitotenv.2016.12.113.

Tsuji, J.S., Lennox, K.P., Watson, H.N., Chang, E.T., 2021. Essential concepts for interpreting the dose-response of low-level arsenic exposure in epidemiological studies. Toxicology 457. https://doi.org/10.1016/J.TOX.2021.152801.

USEPA, 2019. Updated Problem Formulation and Protocol for the Inorganic Arsenic IRIS Assessment.

USFDA, 2022. Arsenic in rice and rice products risk assessment [WWW Document]. URL. https://www.fda.gov/food/cfsan-risk-safety-assessments/arsenic-rice-and-rice-products-risk-assessment.

Van Halem, D., Bakker, S.A., Amy, G.L., Van Dijk, J.C., 2009. Arsenic in drinking water: a worldwide water quality concern for water supply companies. Drink. Water Eng. Sci. 2, 29–34. https://doi.org/10.5194/DWES-2-29-2009.

Vimercati, L., Gatti, M.F., Gagliardi, T., Cuccaro, F., De Maria, L., Caputi, A., Quarato, M., Baldassarre, A., 2017. Environmental exposure to arsenic and chromium in an industrial area. Environ. Sci. Pollut. Res. Int. 24, 11528–11535. https://doi.org/10.1007/S11356-017-8827-6.

WHO, 2011. Arsenic in Drinking-Water, Background Document for Development of WHO Guidelines for Drinking-Water Quality.

WHO, 2018 ([WWW Document). https://www.who.int/news-room/fact-sheets/detail/arsenic.

Witt, B., Ebert, F., Meyer, S., Francesconi, K.A., Schwerdtle, T., 2017. Assessing neurodevelopmental effects of arsenolipids in pre-differentiated human neurons. Mol. Nutr. Food Res. 61, 1700199 https://doi.org/10.1002/mnfr.201700199.

Yager, J.W., Gentry, P.R., Thomas, R.S., Pluta, L., Efremenko, A., Black, M., Arnold, L.L., McKim, J.M., Wilga, P., Gill, G., Choe, K.Y., Clewell, H.J., 2013. Evaluation of gene expression changes in human primary uroepithelial cells following 24-hr exposures to inorganic arsenic and its methylated metabolites. Environ. Mol. Mutagen. 54, 82–98. https://doi.org/10.1002/EM.21749.

Yusà, V., Pérez, R., Sánchez, A., Pardo, O., Roca, M., 2018. Exposure and risk assessment to arsenic species in Spanish children using biomonitoring. Sci. Total Environ. 628–629, 302–309. https://doi.org/10.1016/j.scitotenv.2018.01.330.