

1 Prioritized substance group: Arsenic

Responsible author	Wojciech Wasowicz	Email	wojciech.wasowicz@imp.lodz.pl
Short Name of Institution	NIOM	Phone	(+48) 42 63 14 503
Co-authors	Beata Janasik		

1.1 Background Information

Arsenic (As) is a significant global environmental toxicant. As contamination of soil and drinking water is a problem threatening human health all over the world. Humans are exposed to As through the intake of air, food and water, and occupational exposure occurs in several industries including gold mining and smelting operations. Arsenic is carcinogenic (Group 1 IARC), studies confirming the carcinogenesis of arsenic in humans are identified, but are not reviewed in detail. It is well established that chronic exposure to As is associated with skin, lung and bladder cancers (IARC 1984; 2012, 2014; Helene et al. 2007; Järup et al. 1989; Lauwerys et al. 2001) as well as vascular diseases and hepatotoxicity (NRC 2001). For the general population, the principal route of exposure to arsenic is likely to be the oral route, primarily in the food and in the drinking water. The daily intake of total arsenic from food and beverages is generally in the range of 20–300 mcg/day. Therefore, assessment of exposures from natural sources of inorganic arsenic from diet, water and air would be helpful for risk communication and public health decision-making. Recent attention has also been directed at children's exposure to arsenic and potential health risks, because children are the most vulnerable and sensitive group to the adverse effects of arsenic. Understanding how arsenic exposures from human activities compare to natural background exposures is important for communicating the relative magnitude of calculated risks in perspective with everyday exposures. A number of issues are still to be addressed in HBM for arsenic: selection of exposure biomarkers, the role of genetic polymorphisms in contributing to population variability in pharmacokinetics and sensitivity to the adverse effects of exposure to arsenic etc.

This scoping document focuses on environmental exposure to arsenic (inorganic), which poses the greatest risk for human health.

1.1.1 Hazardous properties

Arsenic (metallic As, CAS numer: 7440-38-2; EC number: 231-148-6). Arsenic is a ubiquitous element that ranks 20th in abundance in the earth's crust.[Mandal & Suzuki 2002]. Arsenic is classified as a metalloid. Elemental arsenic is a steel grey solid material. Arsenic in the environment is combined with other elements such as oxygen, chlorine, and sulfur, and is called as inorganic arsenic. Of the inorganic arsenic compounds, arsenic trioxide, sodium arsenite and arsenic trichloride are the most common trivalent compounds, and arsenic pentoxide, arsenic acid and arsenates (e.g. lead arsenate and calcium arsenate) are the most common pentavalent compounds.(WHO 2000, ASTDR 2007)

Common organic arsenic compounds include arsanilic acid, methylarsonic acid, dimethylarsinic acid (cacodylic acid), and arsenobetaine (WHO, 2000).

Most inorganic and organic arsenic compounds are white or colorless powders that do not evaporate. They have no smell, and most have no special taste. [ASTDR 2007]. Arsenic in its most recoverable form is found in various types of metalliferous deposits. It is common in iron pyrite, galena, chalcopyrite and less common in sphalerite. The most common arsenic mineral is arsenopyrite [Mandal & Suzuki 2002].

The primary use of arsenic is in alloys of lead. Arsenic is a common n-type dopant in semiconductor electronic devices, and the optoelectronic compound gallium arsenide is the second most commonly used semiconductor after doped silicon. Arsenic and its compounds, especially the trioxide, are used in the production of pesticides, treated wood products, herbicides, and insecticides. Although arsenic can be poisonous in higher doses, it has also been used in some medicines. A form of arsenic is still used to treat an uncommon blood cancer known as *acute promyelocytic leukemia*. [Grund et al. 2008]

According to the International Agency for Research on Cancer (IARC), arsenic is classified in Group 1 (*sufficient evidence of carcinogenicity* in humans) In contrast to organic arsenic, iAs is extremely toxic and current risk assessments of dietary exposure to arsenic are entirely based on the inorganic forms. The general population is exposed to iAs via the diet, with food being the major contributor to intake when arsenic concentrations in water are <10 µg/L (the WHO guideline value for drinking water), while drinking water becomes the major source of exposure to iAs when water with arsenic concentrations well above 10 µg/L is used for drinking and cooking (EFSA, 2014; FAO/WHO, 2011). The IARC has established a causal role for oral exposure to iAs on skin, lung, and bladder cancers, and has shown suggestive evidence for liver, kidney, and prostate cancers (IARC, 2012). Apart from cancer – and skin lesions (EFSA, 2014) – a wide range of other adverse health effects such as cardiovascular diseases, developmental toxicity, abnormal glucose metabolism, type II diabetes and neurotoxicity are likely related to chronic ingestion of iAs (FAO/WHO, 2011). Susceptibility to the toxic effects of iAs varies considerably between individuals and populations depending on variations in iAs metabolism related to such factors as age, gender, life stage (e.g. pregnancy, lactation), nutritional status, and genetic polymorphisms in the regulation of enzymes responsible for iAs biotransformation (EFSA, 2014).

1.1.1.1 Knowledge gaps

The assessment of occupational exposure to inorganic arsenic iAs or/and sum of inorganic As is relatively well known (Janasik et al. 2014, Appostoli and al. 1999, Hakala and Pyy 1995,). The effects of general population exposure mainly concern exposure to As with potable water with an As content above 50 µg/L and concern mainly non-European populations. There is little work on the assessment of exposure to drinking water with concentrations below the limit and dietary As intake for European general populations.

Key epidemiologic evidence for risk assessment of dietary iAs comes from populations chronically exposed to high arsenic levels in drinking water (>50 µg/L) in several countries, including southwestern Taiwan (Chen et al., 2010), Bangladesh (Kurokawa et al., 2001), northern Chile (Smith et al., 1998), and Argentina (Hopenhayn-Rich et al., 1998). The main source of As in the diet is organic As compounds such as arsenobetaine, which, is generally assumed to be of no toxicological concern (FAO/WHO, 2011). Dimethylarsinic acid (DMA) – and in traces monomethylarsinic acid (MMA) – are present in various foods, including rice, other plant-derived food and seafood. In vivo studies have shown adverse effects on the urinary bladder, kidneys, thyroid, and foetal development for DMA, whereas the gastrointestinal tract is the primary target organ of MMA (US FDA, 2016). The studies in animals showed a carcinogenic potential for DMA; however the data regarding human carcinogenicity are inconclusive, hence IARC classified these methylated forms as possibly carcinogenic to humans (Group 2B) (IARC, 2012). Arsenosugars and arsenolipids are mainly metabolized in humans to DMA, and limited albeit growing information is available regarding their toxicity (Taylor et al., this issue).

Along with MMA and DMA, these compounds have been proposed to be classified as 'potentially toxic' from a food safety perspective, in contrast to the innocuous arsenobetaine (Feldmann and Krupp, 2011). (Quoted by Cubadda et al 2017).

As a result, exposure levels for iAs with no appreciable health risk, i.e. a tolerable daily or weekly intake, cannot be identified. Instead, reference points for health protection are currently based on benchmark responses of a given percentage of extra risk from human data. A benchmark dose lower confidence limit (BMDL) for 0.5% excess risk of lung cancer has been established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (BMDL0.5 = 3 µg/kg bw/day) (FAO/WHO, 2011), whereas the European Food Safety Authority (EFSA) identified a range of BMDL values for 1% excess risk of cancers of the lung, skin and bladder, as well as skin lesions (BMDL01 = 0.3-8 µg/kg bw/day) (EFSA, 2009). Therefore, for risk characterization an assessment of the margins of continues to emerge exposure (MOEs) between the identified reference points and the estimated daily dietary exposure to iAs is required, since there are no exposure levels associated with the absence of appreciable health risk on long-term (lifetime) basis (Quoted by Cubadda et al 2017).

EFSA and JECFA data assessments are relatively recent, new scientific evidence of adverse effects for populations chronically exposed to iAs via drinking water in concentrations below 50 µg/L, are discussed by other authors (D'Ippoliti et al., 2015; Leonardi et al., 2012; Garcia-Esquinas et al., 2013; Moon et al., 2013; Zheng et al., 2013). Such evidence has not fed into a new risk assessment yet.

The category proposed for arsenic and its inorganic compounds is Category B, as 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. Identified data gaps may vary from spatial gaps in HBM measurement data, to gaps in exposure sources and pathways. Inorganic arsenic is regulated as to drinking water and OELs. There is a toxicological concern because of carcinogenicity and suggested reproductive and neurodevelopmental toxicity of arsenic, as well as the low dose effects that relate to cardiovascular diseases, insulin resistance, type-2 diabetes and hypertension. [NRC 2014; Nachman et al 2017; Navas-Acien et al 2005, 2006; Abhyankar et al 2012].

1.1.2 Exposure characteristics

1.1.2.1 Environmental behaviour

Arsenic is found in the environment in the metallic form and in various inorganic and organic complexes. The sources are both natural and anthropogenic.

Soil: Arsenic occurs naturally in soils as a result of the weathering of the parent rock. Anthropogenic activity has resulted in the widespread atmospheric deposition of arsenic the burning of coal and the smelting of non-ferrous metals including copper [EPA 2009a]. The levels of arsenic in the soils of various countries are said to range from 0.1 to 40 mg/kg (mean 6 mg/ kg), 1 to 50 mg/kg (mean 6 mg/kg) and mean 5 mg/kg but varies considerably among geographic regions. Arsenic is present in soils in higher concentrations than those in rocks [Mandal & Suzuki 2002]. Uncontaminated soils usually contain 1–40 mg/kg of arsenic, with lowest concentrations in sandy soils and those derived from granites, whereas larger concentrations are found in alluvial and organic soils. Arsenate reportedly binds strongly to iron and manganese oxides, and therefore remains in the surface soil layer after deposition [ATSDR, 2007]. Arsenic was observed to be still concentrated after 15 years in the top 20–40 cm of orchard soils treated with lead arsenate (Merwin et al. 1994). However, several experimental studies have found that arsenate can be released from iron oxides at alkaline pH as a result of desorption processes [IPCS, 2001; ATSDR, 2007].

Water: Arsenic is found at low concentration in natural water. The maximum permissible concentration of arsenic in drinking water is 50 mcg/l and recommended value is 10 mcg/l by EPA and WHO [IPCS 2001]. The seawater ordinarily contains 0.001–0.008 mg/l of arsenic. The concentration of arsenic in unpolluted fresh waters typically ranges from 1–10 g/l, rising to 100–5000 g/l in areas of sulfide mineralization and mining [Mandal & Suzuki 2002].

Only a very minor fraction of the total arsenic in the oceans remains in solution in seawater, as the majority is sorbed on to suspended particulate materials. The high levels of arsenic are in waters from areas of thermal activity in New Zealand up to 8.5 mg/l. Geothermal water in Japan contains 1.8–6.4 mg/l and neighboring streams about 0.002 mg/l. Although normally groundwater does not contain methylated form of arsenic but lake and pond waters contain arsenite, arsenate as well as methylated forms, i.e. MMA and DMA [Mandal & Suzuki 2002].

Air: In air, arsenic exists predominantly adsorbed on particulate matters, and is usually present as a mixture of arsenite and arsenate, with the organic species being of negligible importance except in areas of arsenic pesticide application or biotic activity [Mandal & Suzuki 2002]. The human exposure of arsenic through air is generally very low and normally arsenic concentrations in air ranges from 0.4 to 30 ng/m³. According to USEPA the estimated average national exposure in the U.S. is at 6 ng As/m³. Absorption of inhaled arsenic ranges between 30 and 85%, depending on the relative portions of vapour and particulate matters. USEPA estimates that the general public will be exposed to a range of approximately 40–90 ng per day by inhalation. The amount of arsenic inhaled per day is about 50 ng or less (assuming that about 20 m³ of air is inhaled per day) in unpolluted areas. The daily respiratory intake of arsenic is approximately 120 ng of which 30 ng would be absorbed. Typical arsenic levels for the European region are currently quoted as being between 0.2 and 1.5 ng/m³ in rural areas, 0.5 and 3 ng/m³ in urban areas and no more than 50 ng/m³ in industrial areas. [European Commission 2000]

Animals and human beings: As in plant tissue, arsenic is cumulative in animal tissue, allowing for a wide variation in concentration due to the variance in arsenic ingested in different areas. Among marine animals, arsenic is found to be accumulative to levels of from 0.005 to 0.3 mg/kg in coelenterates, some molluscs and crustaceans. Some shellfish may contain over 100 mcg/g of arsenic. The average arsenic content in freshwater fish is of 0.54 mcg/g on the basis of total wet weight, but some values reach as high as 77.0 mcg/g in the liver oil of freshwater bass. In mammals it is found that the arsenic accumulates in certain areas of the ectodermic tissue, primarily the hair and nails [Mandal & Suzuki 2002].

Human exposure: Humans are exposed to many different forms of inorganic and organic arsenic species (arsenicals) in food, water and other environmental media. Each of the forms of arsenic has different physicochemical properties and bioavailability and therefore the study of the kinetics and metabolism of arsenicals is a complex matter.

General population: For the general population, the principal route of exposure to arsenic is likely to be the oral route, primarily via food, and drinking water. Intake from air, is usually much less. Dermal exposure can occur, but is not considered a primary route of exposure. The epidemiologic evidence for an across the placenta is insufficient, although there exists limited evidence for arsenic concentrations found in cord blood and maternal blood of maternal-infant pairs exposed to high arsenic-containing drinking water. [ASTDR 2007.]

Occupational exposure population: Occupational exposure to arsenic may be significant in several industries, mainly nonferrous smelting, arsenic production, wood preservation, glass manufacturing. Occupational exposure would be via inhalation and dermal contact.

Human biomonitoring (HBM)

HBM can be defined as “the method for assessing human exposure to chemicals or their effects by measuring these chemicals, their metabolites or reaction products in human specimens [CDC, 2005]. Biomonitoring data directly reflect the total body burden or biological effect resulting from all routes of exposure, and interindividual variability in exposure levels, metabolism and excretion rates.

The cytotoxicity and metabolism of arsenic is a function of its oxidation state and methylation status [Cohen et al. 2007]. Metabolic conversion of inorganic arsenic into methylated products is a multistep process that yields mono-, di-, and trimethylated arsenicals. In recent years, it has become apparent that formation of methylated metabolites of inorganic arsenic is not necessarily a detoxification process. Products formed in this pathway may be more reactive and toxic than inorganic arsenic [Thomas et al. 2007]. Inorganic arsenic are commonly methylated in liver in the presence of a methyl donor S-adenosylmethionine (SAM) and a co-factor glutathione (GSH) with arsenomethyltransferase (As3MT) to relevant monomethylated [e.g., monomethylarsonous acid (MMA^{III}) monomethylarsonic acid (MMA^V)] and dimethylated arsenic metabolites [e.g., dimethylarsinous acid (DMA^{III}), dimethylarsinic acid (DMA^V)], and finally excreted into urine [Vahter et al. 1999; Vahter 2002]. Recently, a reductive methylation pathway has also been described [Tseng 2009]. Following arsenic exposure, 40 to 60% of arsenic intake is eliminated through urine. It should also be mentioned that the majority of the environmentally exposed population groups studied so far have on average 10-30% of inorganic As, 10-20% of MMA and 60-70% of DMA in urine, but considerable inter-individual variations have been observed, which may be a result of genetic polymorphism in the methylation capacity of arsenic (Vahter 1999).

Urinary levels of arsenic are generally regarded as a good measure and biomarker of exposure, although measurements of total arsenic in urine do not contain information concerning arsenic species, thereby complicating the assignment of toxicity and potential health risk to various species of As. Quantitative determination of the amount of a specific element is particularly important and that is why speciation methods are considered essential for drawing accurate conclusions in arsenic exposure and risk assessment.

For many years, biological monitoring of exposure to arsenic has been based on the determination of the sum of iAs and methylated metabolites DMA and MMA in urine. Novel biomonitoring methods (speciation analysis) are usually tested and validated in research settings (Janasik et al. 2014). Sustained national and international surveillance programmes typically use well established biomonitoring techniques (e.g. biomarkers which are known to reflect exposure to the chemical of interest, standardized sampling methods and verified analytical techniques) to collect information on population exposures to environmental hazards that are known to be significant to public health.

A summary of available human biomonitoring from EU countries on arsenic exposure are summarized in a report from the World Health Organization (2015) and are shown in the table below.

Table 1.1: Summary of available HBM data on arsenic (toxicologically relevant species including inorganic arsenic and its metabolites) Geometric means (GM) or percentiles (P90/P95) are indicated.

Country	Study	Population (N)	Total arsenic			TRA species		references
			Blood (ng/mL)	Urine		Urine (µg/g creat.)		
				(µg/g creat.)	(µg/L)			
Belgium (Flanders)	FLESH (2007-2011)	Neonates (241)	0.54 GM 2.18 P90	-	-	-	Schoeters et al., 2012a	
		Mothers Age: 20-40 y (235)	0.64 GM 2.04 P90	15.9 GM 71.4 P90	-	3.7 GM 10.7 P90		
		Adolescents Age: 14-15 y (207)	0.62 GM 2.12 P90	9.3 GM 49.0 P90	-	3.6 GM 8.0 P90		
Germany	Environmental Specimen Bank (2000-2017), four sampling locations	Young adults Age: 20-29 y		4.4- 5.5 GM			www.umweltprobenbank.de (2017)	
	GerES I (1985-86)	Adults Age: 25-69 y (2542)	-	-	9.02 GM 37.5 P95	-	Kolossa-Gehring et al., 2012; Schulz et al., 2007b	
	GerES II (1990-92)	Adults Age: 18-79 y (4001)	0.5 GM 2.0 P95	-	6.33 GM 30.2 P95	-		
		Children Age: 6-17 y (731)	0.33 GM 1.4 P95	-	6.01 GM 27.5 P95	-		
	GerES III (1998)	Adults Age: 18-69 y (4052)	0.61 GM 2.4 P95	-	3.87 GM 19.3 P95	-		
	GerES IV (2003-2006)	Children Age: 3-14 y (1734)	0.23 GM 0.3 P90	-	4.4 GM 11.0 P90	-		
France	ENNS (2006-2007)	Adults 18-74 y (1515)	-	11.96 GM 61.29 P95	-	3.34 GM 8.9 P95	Frery et al., 2012	
Italy	PROBE (2008-2010)	Adolescents Age: 13-15 y (252)	0.82 GM 3.69 P95	-	-	-	Pino et al., 2012	
Slovenia	National HBM Survey (2007-2009)	Adults Age: 20-40 y (274)	0.74 GM 2.98 P95	-	-	-	Snoj Tratnik, Mazej & Horvat, 2012	

1.1.2.2 Health based guidance values available for HBM data

1.1.2.2.1 General population

The following table summarizes the available reference values for Canadian and German population.

Table 1.2: Reference values (RV95) for arsenic in blood and urine based on human biomonitoring data

	Population	Group (years)	Years (N)	P95 (95% CI) (µg/L)	RV95 (µg/L)	References
arsenic (total) in blood	Canadian	6-19	2007-2009 (875)	1.4 (1.0-1.8)	1.4	Saravanabhavan et al. (2017)
arsenic (total) in blood	Canadian	20-79	2007-2009 (996)	2.0 (1.8-2.2)	2.0	
Arsenic (total) in urine	German	3-14*	2003-2006		15.0	Schultz et al.(2011)
Arsenic (total) in urine	German	18-69*	1997-1999		15.0	

* for children and adults who did not eat fish during 48 hours prior to sample collection

The RV 95 for total arsenic in urine, according to the findings of the German HBM survey, is 15 µg/L for children and adults who did not eat fish during 48 hours prior to sample collection [Schulz et al., 2011]. The GM levels of total arsenic in European populations were from 0.5 µg/L to 1 µg/L in blood and from 4µg/g to 16 µg/g creatinine in urine. There was no obvious difference observed between children/adolescents and adults.[WHO 2015]

In order to establish representative human biomonitoring data for the Canadian general population, an extensive HBM component has been incorporated into the Canadian Health Measures Survey (CHMS). The CHMS, which was launched in 2007, is the most comprehensive direct health measures survey conducted in Canada and is designed to provide nationally-representative data on indicators of environmental exposures, health and nutritional status, and related risks and protective characteristics [Tremblay et al., 2007].

1.1.2.2.2 Occupational population

The following recommendations are available:

Table 1.3: Recommended Biological Limit Values (BLV) for occupational exposure

Organization	Biological Limit Value (BLV)	Reference
Germany/ Deutsche Forschungsgemeinschaft (DFG)	<ul style="list-style-type: none"> Inorganic arsenic and methylated metabolites BLW 50 mcg/l Arsenic(+III) BAR 0.5 mcg/l Arsenic(+V) BAR 0.5 mcg/l Monomethylarsonic acid BAR 2 mcg/l Dimethylarsinic acid BAR 10 mg/l 	DFG 2016
USA/ ACGIH	<ul style="list-style-type: none"> 35 mcg arsenic/L of urine (inorganic arsenic plus methylated metabolites) 	ACGIH

BAR ("Biologische Arbeitsstoff-Referenzwerte") describe the background level of a substance which is present concurrently at a particular time in a reference population of persons of working age who are not occupationally exposed to this substance. The BAR are based on the 95th percentile without regarding effects on health.

BLW ("Biologischer Leit-Wert") is the amount of a chemical substance or its metabolites or the deviation from the norm of biological parameters induced by the substance in exposed humans which serves as an indicator for necessary protective measures. BLWs are assigned only for hazardous materials for which the available toxicological or occupational-medical data are insufficient for the establishment of BAT values[DFG 2016]

1.1.3 Policy relevance

1.1.3.1 European Policies

European legislations concerning arsenic are described below.

1.1.3.2 Food safety

Maximum levels for arsenic in certain foods have been established by [Commission Regulation \(EC\) No 2015/1006](#) (future section 3.5 of the Annex to Regulation (EC) No 2006/1881, applicable from 1 January 2016 onwards).

The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) assessed the risks to human health related to the presence of arsenic in food. More than 100,000 occurrence data on arsenic in food were considered with approximately 98 % reported as total arsenic. Making a number of assumptions for the contribution of inorganic arsenic to total arsenic, the inorganic arsenic exposure from food and water across 19 European countries, using lower bound and upper bound concentrations, has been estimated to range from 0.13 to 0.56 µg/kg bodyweight (b.w.) per day for average consumers, and from 0.37 to 1.22 µg/kg b.w. per day for 95th percentile consumers. Dietary exposure to inorganic arsenic for children under three years of age is in general estimated to be from 2 to 3-fold higher that of adults. The CONTAM Panel concluded that the provisional tolerable weekly intake (PTWI) of 15 µg/kg b.w. established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is no longer appropriate as data had shown that inorganic arsenic causes cancer of the lung and urinary bladder in addition to skin, and that a range of adverse effects had been reported at exposures lower than those reviewed by the JECFA. The CONTAM Panel modelled the dose-response data from key epidemiological studies and selected a benchmark response of 1 % extra risk of cancers of the lung, skin and bladder, as well as skin lesions (BMDL₀₁ = 0.3-8 µg/kg bw/day). The estimated dietary exposures to inorganic arsenic for average and high level consumers in Europe are within the range of the BMDL₀₁ values identified, and therefore there is little or no margin of exposure and the possibility of a risk to some consumers cannot be excluded.

1.1.3.3 Chemicals

Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006, concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals, Official Journal No. L 396/1 of 30.12.2006 (hereinafter "REACH") aims at ensuring a high level of protection for human health and environment, while promoting the efficient functioning of the EU internal market and stimulating innovation and competitiveness in the chemical industry.

Having a common interest in fulfilling the requirements under REACH, the members of the As Consortium have therefore created the As Consortium back in 2009, in order to share human and financial resources involved in complying with REACH.

The following substances were REACH registered with the help of the As consortium:

Name	Molecular formula	EC	CAS	Registered	No of registrants	LR	Authorisation
Arsenic metal	As	231-148-6	7440-38-2	yes		ppm	
Arsenic trichloride	AsCl ₃	232-059-5	7784-34-1	yes		ppm	
Diarsenic trioxide	As ₂ O ₃	215-481-4	1327-53-3	yes	6	umicore	Boliden/nordenhamer/ zinhutte/linxens Fr
Gallium arsenide	GaAs	215-114-8	1303-00-0	yes	3	FCM	
Trilead diarsenate	Pb ₃ (AsO ₄) ₂	222-979-5	3687-31-8	Yes, INACTIVE	1		
Calcium arsenate	Ca ₃ (AsO ₄) ₂	231-904-5	7778-44-1	Yes, INACTIVE	1		
Tricopper arsenide	Cu ₃ As	234-472-6	12005-75-3	Yes, INACTIVE	1		

**The Arsenic consortium, was founded in 2009(members are producers and importers of arsenic and arsenic compounds). The Consortium Members controle complying with the requirements of the REACH Regulation in respect of the substance(s) covered by the Consortium and to follow up on environment, health and safety (EHS) regulations related to arsenic and arsenic compounds. The consortium includes, among others: UMICORE (Belgium),AURUBIS (Germany) and Boliden Harjavalta Oy (Finland)*

According to the harmonised classification and labelling (CLP) approved by the European Union, this substance is toxic if swallowed, is toxic if inhaled, is very toxic to aquatic life and is very toxic to aquatic life with long lasting effects. Moreover, some uses of this substance are restricted under Annex XVII of REACH.

Occupational health and safety

Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. This proposal aims to improve workers' health protection by reducing occupational exposure to five carcinogenic chemical agents, to provide more clarity for workers, employers and enforcers, and to contribute to a level playing field for economic operators.

1.1.4 Technical aspects

1.1.4.1 Availability of biomarkers and methods

There are several potential biomarkers for arsenic exposures. Preferred biomarkers are determination of As and its chemical forms in urine. Non-invasive, ease collection and because the majority of absorbed arsenic and its metabolites is eliminated via urine puts this type of markings in a privileged position. Moreover, the analytical techniques allows arsenic speciation in urine, but not hair and nails (due to mineralization). The short half-life of inorganic and organic arsenic species in blood and invasive collection limits the utility of arsenic biomarkers in blood, similar to determination As in hair and nails. Advantages for this these biomarkers in hair and nails are is assessment of integrated exposures, but these markers include arsenic derived from all way organic arsenic (non-toxic) and inorganic species. (Hughes 2006; Navas-Acien and Guallar, 2008). When exposure to a compound results in multiple biomarkers and the mode of action is not known with certainty, it is recommended to sum as many of the metabolites in a Biomonitoring Equivalent (BE) calculation as long as the metabolites are specific to exposures of concern (Aylward et al., 2009). Sum of iAs, MMA, DMA correlate well with drinking water concentration (Calderon et al., 1999; Hall et al., 2006) or estimated daily dose calculated using drinking water concentrations (Navas-Acien et al., 2009; Agusa et al., 2009). The concentrations of total arsenic and iAs, MMA, and DMA are all fairly constant over time with small intra-individual variabilities (Navas-Acien et al., 2009; Kile et al., 2009). First morning voids of total arsenic are indicative of and correlated with subsequent voids throughout the day (Calderon et al., 1999). For these reasons, speciated arsenic in urine (iAs III, iAs V, MMA, and DMA) are the preferred biomarker(s) for exposures to inorganic arsenic (Lauwerys and Hoet, 2001) but as described Buchet et al., 1994 certain types of seafood can contain small quantities of DMA than the urine sample should abstain from eating seafood for 3–4 days prior to urine collection (Lauwerys and Hoet, 2001). In such cases where diet cannot be controlled, Lauwerys and Hoet (2001) have recommended using iAs concentration in urine as opposed to the sum of iAs, MMA, and DMA in urine as the biomarker of choice. Since MMA is not affected by seafood consumption, both iAs and MMA should be reliable biomarkers of inorganic arsenic exposures. Then, the recommendations are for using sums of all three (iAs, MMA, and DMA) as a biomarkers for As .when no exposures to seafood have occurred.

The determination of arsenic in biological specimens requires sensitive analytical methods, performed under good quality control conditions. Various methods exist that differ in sample preparation technique and/or the detections system. Determination of total As concentration can be done by ICP MS, inorganic arsenic as well as MMA and DMA can be done by AAS technique with hydrogen generation.

Speciation of arsenic requires coupled analytical techniques (ICP-MS-HPLC) and procedures and expensive reagents and equipment, which are not routinely available in analytical laboratories. Speciation analysis is necessary to differentiate between inorganic and organic arsenic exposure.

Need for new approaches

The symptoms and signs caused by long-term elevated exposure to inorganic arsenic differ between individuals, population groups and geographical areas. Thus, there is no universal definition of the disease caused by arsenic. This complicates the assessment of the burden on health of arsenic.

There is a need to harmonize exposure biomarkers and to validate biomarkers of susceptibility, selection of exposure biomarkers, and include the role of genetic polymorphisms in contributing to population variability in pharmacokinetics and sensitivity to the adverse effects of exposure to arsenic.[Ladeira C, Viegas S. 2016; Chen et al. 2005; Janasik et al. 2018]

It is important to harmonize the approaches used to investigate different study populations. The selection of best suited matrices and biomarkers of exposure is crucial. Markers of susceptibility need to be validated. These are important for understanding the human health effects of low-level As exposure as a basis for future research efforts, risk assessment, and exposure remediation policies worldwide. As speciation in urine, would provide characterization of species-specific exposure at levels relevant for European population. In recent years interest in gene-environment interaction has grown substantially, because of the progress in laboratory techniques, improved understanding of genetics and realization of complex mechanisms between genetics and environment. Identification and validation of novel biomarkers of susceptibility is therefore an important part in investigation of exposure-health relationships.

1.1.5 Societal concern

Arsenic is one of WHO's 10 chemicals of major public health concern. The effects of arsenic toxicity on mental health and associated social consequences have not been well reported and hence more scientific attention is needed.

Arsenic contamination of groundwater is widespread and there are a number of regions where arsenic contamination of drinking-water is significant. It is now recognized that at least 140 million people in 50 countries have been drinking water containing arsenic at levels above the WHO provisional guideline value of 10 µg/L .

In 2010, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) re-evaluated the effects of arsenic on human health, taking new data into account. JECFA concluded that for certain regions of the world where concentrations of inorganic arsenic in drinking-water exceed 50–100 mcg/L, there is some evidence of adverse effects. In other areas, where arsenic concentrations in water are elevated (10–50 µg/L), JECFA concluded that while there is a possibility of adverse effects, these would be at a low incidence that would be difficult to detect in epidemiological studies.

The most important action in affected communities is the prevention of further exposure to arsenic by the provision of a safe water supply for drinking, food preparation and irrigation of food crops.

WHO's work to reduce arsenic exposure includes setting guideline values, reviewing evidence, and providing risk management recommendations. WHO publishes a guideline value for arsenic in its *Guidelines for drinking-water quality*. The Guidelines are intended for use as the basis for regulation and standard setting worldwide.

The WHO/UNICEF Joint Monitoring Programme for Water Supply, Sanitation and Hygiene monitors progress towards global targets on drinking water. Under the new 2030 Agenda for Sustainable Development, the indicator of “safely managed drinking water services” calls for tracking the population accessing drinking water which is free of faecal contamination and priority chemical contaminants, including arsenic.

Due to its classification as a substance toxic to reproduction (“CRM” according to Annex VI of Regulation 1272/2008) arsenic is included in the “SIN (Substitute It Now!) List”, a comprehensive database of chemicals likely to be restricted or banned in the EU developed by the non-governmental European “International Chemical Secretariat” (ChemSec).

Arsenic ranks 1st out of 275, on the “Substance Priority List” (SPL) prepared biannually by the ATSDR for substances most commonly found at facilities on the National Priorities List (NPL) and which are determined to pose the most significant potential threat to human health due to their known or suspected toxicity and potential for human exposure. **It should be noted that this priority list is not a list of “most toxic” substances, but rather a prioritization of substances based on a combination of their frequency, toxicity, and potential for human exposure at NPL (national priority list) sites.**

In June 2017, members of the Stakeholder Forum provided feedback on the proposed strategy and criteria to be used for the prioritisation of substances for monitoring and research under HBM4EU. Arsenic was voted by stakeholders who participated in the Stakeholder Workshop organized in the frame of HBM4EU in on November 20th 2017 as a “top substance of concern”.

1.2 Categorization of Substances

The proposed category for Arsenic is Category B.

The category proposed for arsenic and its inorganic compounds is **Category B**, as 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. Identified data gaps may vary from spatial gaps in HBM measurement data, to gaps in exposure sources and pathways. Inorganic arsenic is regulated as to drinking water and OELs. There is a toxicological concern because of carcinogenicity and suggested reproductive and neurodevelopmental toxicity of arsenic, as well as the low dose effects that relate to cardiovascular diseases, insulin resistance, type-2 diabetes and hypertension. The effects of chronic exposure to low levels and the factors of susceptibility have not been adequately investigated.

Table 4: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C,D,E substances

Category	Abbreviation/ Acronym	Systematic name	CAS No.	Regulations
B	As	Arsenic	7440-38-2	Regulation (EC) No 1907/2006 REACH Regulation (EC) No 1907/2006 for inclusion of substances in the Authorisation List (Annex XIV)

1.3 Policy-related questions

The following policy-related questions relate to commitments under this frame.

1. What is the current exposure of the EU population to arsenic?
2. What biomonitoring and exposure (environmental and occupational) data on arsenic, relevant to the European population, are currently available?
3. What is the geographic spread of the current exposure and how does it relate to different exposure sources (environmental; dietary sources)?
4. Which population groups are most at risk?
5. What factors (genetic polymorphisms) make people more susceptible or not to the risk of health effects due to arsenic exposure? How are the best and more sensitive biomarkers for identification of reliable arsenic exposure and to link to potential adverse health-effect?
6. What are possible health effects resulting from chronic low exposure to arsenic from food consumption?
7. What are the best analytical methods should allow for differentiating species in urine?
8. How can harmonized, validated and comparable information be collected to support and evaluate current policies?
9. How can transfer of knowledge & technology be facilitated to support current policies?
10. How can HBM4EU results support European policy decisions?

1.4 Research Activities to be undertaken

Table 1.4: Listing of research activities to be carried out to answer the policy questions

Policy question	Substance	Available knowledge	Knowledge gaps and activities needed
What is the current exposure of the EU population to arsenic?	As	Human exposure and effects data are limited.	Mapping and / or updating existing biomonitoring / exposure data - collection, comparison, evaluation and integration into IPChem - identification of knowledge gaps - prioritization of research needs WP 7/8/9/10
What biomonitoring and exposure (environmental and occupational) data on arsenic, relevant to the European population, are currently available.	As	Publications on occupational exposure are available, but the data is rather old and some exposures are not relevant anymore. Publications on environmental exposure are available, but the data is rather not EU population exposures and not included dietary sources (excluded water)	Mapping / updating existing toxicological/biomonitoring data collection, comparison, evaluation and integration into IPChem identification of knowledge gaps WP 7/8/9/10
What is the geographic spread of the current exposure and how does it relate to different exposure sources (environmental; dietary sources)?	As	Human exposure and effects data are limited.	Mapping of existing data on arsenic content in food and water including geographical variations in Europe. The term daily intake of arsenic depending on the geographic region and dietary habit. Use of existing data to assess the determinants of exposure, including geographic variations and their causes (e.g. environmental exposures, diet) identification of knowledge gaps
Which population groups are most at risk?	As	Studies in vulnerable populations and studies for a better understanding of the health effects of inorganic arsenic in the population at exposure levels in EU are greatly needed.	Establish European arsenic biomonitoring program covering broad population groups (children and adults).
What factors (genetic polymorphisms) make people more susceptible or not to the risk of health effects due to arsenic exposure? How is the best and more sensitive biomarkers for identification of reliable arsenic exposure and to link to potential adverse health-effect?	As	Human exposure and effects data are limited. Publications on influence of genetic polymorphisms on arsenic metabolism are available, but the data is rather not EU population exposures.	Mapping of existing capacities - Explore the possible use of existing cohorts for the investigation of the adverse health effects due to chronic exposure to low levels of arsenic including the identification and possibly validation of markers of susceptibility - Identification of reliable biomarkers (biochemical and/or molecular biology markers) of arsenic exposure and to link to potential adverse health-effect
What are possible health effects resulting from chronic low exposure to arsenic from food consumption?	As	Human exposure and effects data are limited.	- Identification of groups at risk of exceeding health-based guidance values, based on existing information (e.g. by age, gender, diet, geography, co-exposures, hot-spots in Europe) - To determine whether current or expected exposure levels of As are of concern for health in the general population.

Policy question	Substance	Available knowledge	Knowledge gaps and activities needed
What is the safe intake level for arsenic that is without any appreciable health risk in the general European population?	As	The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) assessed the risks to human health related to the presence of arsenic in food, but human exposure and effects data are limited.	Preparation of a core study to assess: <ul style="list-style-type: none"> - (a) the current exposure of Europeans to arsenic and the associated risk and to facilitate the assessment of temporal trends with regards to the effectiveness of policies (b) the contributions of different sources (dietary, environmental,) to the body burden, with the aim to elaborate HBM threshold levels for Europe and safe upper limits for different types of foodstuff
What are the best analytical methods should allow for differentiating species in urine?	As	Recently developed HBM analytical methods should allow for differentiating species in urine, resulting from inorganic arsenic exposure, including As III, As V and twomethylated metabolic products, DMA and MMA.	Mapping of existing capacities <ul style="list-style-type: none"> - cost-effective, reliable analytical methods capable of speciation analysis - standard procedures for quality-controlled sampling - qualified laboratories for sample analysis as result of the QA / QC program established in HBM4EU - Arsenic different chemical form of should be included (speciation analysis). Laboratories that will apply for the determination of arsenic in biological material should be verified preceded by participation in the QA / QC program established by HBM4EU. - Establishment of unified methods of biological material collection, storage and shipping procedures to centers, which will determine arsenic concentrations.
How can harmonized, validated and comparable information be collected to support and evaluate current policies?	As		<ul style="list-style-type: none"> - Preparation of an inventory of current relevant national strategies in European countries
How can HBM4EU results support European policy decisions?	As		<ul style="list-style-type: none"> - Identification of stakeholders - Mapping, prioritizing and addressing stakeholder needs, starting with policy makers and scientists - Describe previous studies identifying the impact of EU legislation - Establish permanent European arsenic biomonitoring as support of arsenic european policies

1.5 References

1. Abhyankar L. N. , Jones M.R., Guallar E., and Navas-Acien A.,2012 Arsenic exposure and Hypertension: A systematic Review, *EHP* 120(4), 494-500
2. ACGIH (2014) TLV® and BEIs® based on the documentation of the threshold limit values for chemical substances and physical agents & biological exposure indices. ACGIH®, Cincinnati, OH
3. Agency for Toxic Substances Disease Registry. 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.
4. Agusa, T., Kunito, T., Minh, T.B., Kim Trang, P.T., Iwata, H., Viet, P.H., Tanabe, S., 2009. Relationship of urinary arsenic metabolites to intake estimates in residents of the Red River Delta, Vietnam. *Environ. Pollut.* 157, 396–403.
5. Annual Report of the European Food Safety Authority (EFSA) 2014 Dietary exposure to inorganic arsenic in the European population doi: 10.2903/j.efsa.2014.3597 *EFSA Journal* 2014;12(3):3597
6. 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
7. Arsenic, Environmental Health Criteria 224, Arsenic and Arsenic Compounds; World Health Organisation, Geneva, 2004
8. Aylward, L.L., Hays, S.M., Gagné, M., Krishnan, K., 2009. Derivation of Biomonitoring Equivalents for di(2-ethylhexyl)phthalate (CAS No. 117-81-7). *Regul. Toxicol. Pharmacol.* 55, 249–258.
9. Buchet, J.P., Pauwels, J., Lauwerys, R., 1994. Assessment of exposure to inorganic arsenic following ingestion of marine organisms by volunteers. *Environ. Res.* 66, 44–51
10. Calderon, R.L., Hudgens, E., Le, X.C., Schreinemachers, D., Thomas, D.J., 1999. Excretion of arsenic in urine as a function of exposure to arsenic in drinking water. *Environ. Health Perspect.* 107, 663–667
11. CDC (2005). Third National Report on Human Exposure to Environmental Chemicals. Atlanta, GA: Centers for Disease Control and Prevention.
12. Chen CJ, Hsu LI, Wang CH, Shih WL, Hsu YH, Tseng MP, Lin YC, Chou WL, Chen CY, Lee CY, Wang LH, Cheng YC, Chen CL, Chen SY, Wang YH, Hsueh YM, Chiou HY, Wu MM.2005 Biomarkers of exposure, effects and susceptibility of arsenic- induced health hazards in Taiwan. *Toxicol Appl Pharmacol.*;206(2):198-206.
13. Chen CL, Chiou HY, Hsu LI, Hsueh YM, Wu MM, Chen CJ. Ingested arsenic, characteristics of well water consumption and risk of different histological types of lung cancer in northeastern Taiwan. *Environ Res.* 2010; 110:455–462.
14. Cohen SM, Arnold LL, Beck BD, Lewis AS, Eldan M. Evaluation of the carcinogenicity of inorganic arsenic. *Crit. Rev. Toxicol.* 2013; 43:711–752.
15. Cohen SM, Arnold LL, Eldan M, Lewis AS, Beck BD. Methylated arsenicals: the implications of metabolism and carcinogenicity studies in rodents to human risk assessment. *Crit. Rev. Toxicol* 2006;36(2): 99–133.
16. Commission Regulation (EC) No 2015/1006 (future section 3.5 of the Annex to Regulation (EC) No 2006/1881, applicable from 1 January 2016 onwards
17. Cubadda F, Ciardullo S, D'Amato M, Raggi A, Aureli F, Carcea M. Arsenic contamination of the environment-food chain: a survey on wheat as a test plant to investigate phytoavailable arsenic in Italian agricultural soils and as a source of inorganic arsenic in the diet. *J. Agric. Food Chem.* 2010; 58:10176–10183.
18. Cubadda F, D'Amato M, Aureli F, Raggi A, Mantovani A. Dietary exposure of the Italian population to inorganic arsenic: the 2012-2014 Total Diet Study. *Food Chem. Toxicol.* 2016; 98:148–158.
19. Cubadda F, D'Amato M, Mancini FR, Aureli F, Raggi A, Busani L, Mantovani A. Assessing human exposure to inorganic arsenic in high-arsenic areas of Latium: a biomonitoring study integrated with indicators of dietary intake. *Ann. Ig.* 2015; 27:39–5
20. D'Ippoliti D, Santelli E, De Sario M, Scortichini M, Davoli M, Michelozzi P. Arsenic in drinking water and mortality for cancer and chronic diseases in central Italy, 1990-2010. *PLoS One.* 2015; 10:e0138182.

21. Deutsche Forschungsgemeinschaft (DFG), Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, "List of MAK and BAT Values 2017. Report 53," WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim, 2017.
22. ENVIRONMENT AGENCY, 2009a. Using Soil Guideline Values. Science Report SC050021/SGV introduction. Bristol: Environment Agency. (<http://www.environment-agency.gov.uk/clea>).
23. Environmental Protection Agency . Health assessment document for inorganic arsenic. Research Triangle Park: Environmental Protection Agency; 1983. P. 351.
24. European Chemicals Authority (ECHA), "Information on Chemicals -- Harmonized Classification -- Annex VI of Regulation (EC) 1272/2008 (CLP)," [Online]. Available: <https://echa.europa.eu/el/information-on-chemicals/cl-inventory-database/-/discli/details/15915>. [Accessed 15 10 2018].
25. EUROPEAN COMMISSION, 2000, European Commission Working Group on Arsenic, Cadmium and Nickel Compounds. Ambient air pollution by As, Cd and Ni compounds. Position Paper, October 2000. Available at: http://europa.eu.int/comm/environment/air/pdf/pp_as_cd_ni.pdf
26. Feldmann J, Krupp EM. 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.* 2011; 399:1735–1741.
27. Food and Agriculture Organization of the United Nations World Health Organization (JECFA) JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES 2011
28. Frery N, Vandentorren S, Etchevers A, Fillol C (2012). Highlights of recent studies and future plans for the French human biomonitoring (HBM) programme. *Int J Hyg Environ Health*, 215(2):127–32.
29. García-Esquinas E, Pollán M, Umans JG, Francesconi KA, Goessler W, Guallar E, Howard B, Farley J, Best LG, Navas-Acien A. Arsenic exposure and cancer mortality in a US-based prospective cohort: the strong heart study. *Cancer Epidem. Biomar.* 2013; 22:1944–1953.
30. 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.a03_113.pub2
31. Hakala E, Pyy L (1995) Assessment of exposure to inorganic arsenic by determining the arsenic species excreted in urine. *Toxicol Lett* 77:249–258. doi:10.1016/0378-4274(95)03304-1
32. HallHall, M., Chen, Y., Ahsan, H., Slavkovich, V., van Geen, A., Parvez, F., Graziano, J., 2006. Blood arsenic as a biomarker of arsenic exposure: results from a prospective study. *Toxicology* 225, 225–233.
33. Helene CH, Chon J, Fowler A (2007) Arsenic. In: Nordberg GF, Fowler BA, Nordberg M, Friberg LT (eds) *Handbook on the toxicology of metals*, 3rd edn. Elsevier, Amsterdam, pp 367–406
34. Hopenhayn-Rich C, Biggs ML, Smith AH. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. *Int. J. Epidemiol.* 1998; 27:561–569.
35. IARC (1987) Monographs on the evaluation of carcinogenic risk to humans. Overall valuations of carcinogenicity: an updating of IARC. Lyon, Supplement 7: 100
36. IARC. 2012. Arsenic, metals, fibres, and dusts. International Agency for Research on Cancer. *IARC Monogr Eval Carcinog Risks Hum* 100(Pt C):11-465.
37. IARC. 2014. Agents classified by the IARC monographs. Volumes 1–111. Lyon, France: International Agency for Research on Cancer. <http://monographs.iarc.fr/ENG/Classification/ClassificationsCASOrder.pdf>. September 9, 2014.
38. Janasik B., Reszka E., Stanislawska M., Jablonska E., Kuras R., Wiczorek E., Malachowska B., Fendler W., Wasowicz W. 2018, Effects of arsenic exposure on NRF2-KEAP1 Pathway and Epigenetic Modification. *Biol Trace Elem Res* 185(1), 11-19
39. Janasik, B., Reszka, E., Stanislawska, M., Wiczorek, E., Fendler, W., & Wasowicz, W. (2014). Biological monitoring and the influence of genetic polymorphism of As3MT and GSTs on distribution of urinary arsenic species in occupational exposure workers. *International Archives of Occupational and Environmental Health*, 88, 807–818.
40. Järup L, Pershagen G, Wall S (1989) Cumulative arsenic exposure and lung cancer in smelter workers: a dose-response study. *Am J Ind Med* 15:31–41. Doi:10.1002/ajim.4700150105
41. Kile, M.L., Hoffman, E., Hsueh, Y.M., Afroz, S., Quamruzzaman, Q., Rahman, M., Mahiuddin, G., Ryan, L., Christiani, D.C., 2009. Variability in biomarkers of arsenic exposure and metabolism in adults over time. *Environ. Health Perspect.* 117, 455–460
42. Kolossa-Gehring M, Becker K, Conrad A, Schroter-Kermani C, Schulz C, Seiwert M (2012). Environmental surveys, specimen bank and health related environmental monitoring in Germany. *Int J Hyg Environ Health*, 215(2):120–6.

43. Kurokawa M, Ogata K, Idemori M, Tsumori S, Miyaguni H, Inoue S, Hotta N. Investigation of skin manifestations of arsenicism due to intake of arsenic-contaminated groundwater in residents of Samta, Jessore, Bangladesh. *Arch. Dermatol.* 2001; 137:102–103.
44. Ladeira c., Viegas S. 2016 Human Biomonitoring – An overview on biomarkers and their application in Occupational and Environmental Health; *Biomonitoring* 3:15-24 ;De Gruyter
45. Lauwerys R, Hoet P (2001) Industrial chemical exposure –guidelines for biological monitoring, 3rd edn. Lewis Publishers, CRC Press, Boca Raton, FL, pp 36–49
46. Leonardi G, Vahter M, Clemens F, Goessler W, Gurzau E, Hemminki K, Hough R, Koppova K, Kumar R, Rudnai P, Surdu S, Fletcher T. Inorganic arsenic and basal cell carcinoma in areas of Hungary, Romania, and Slovakia: a case-control study. *Environ. Health Persp.* 2012; 120:721–726.
47. Mandal B.K., Suzuki K.T. (2002) Arsenic round the world: a review, *Talanta* 58, pp 201-235
48. Merwin, I.A., W.C. Stiles, and H.M. van Es. 1994. Orchard groundcover management impacts on soil physical properties. *J. Amer. Soc. Hort. Sci.* 119:216–222.
49. Michael F. Hughes Biomarkers of Exposure: A Case Study with Inorganic Arsenic *Environ Health Perspect.* 2006 Nov; 114(11): 1790–1796.
50. Moon KA, Guallar E, Umans JG, Devereux RB, Best LG, Francesconi KA, Goessler W, Pollak J, Silbergeld EK, Howard BV, Navas-Acien A. Association between exposure to low to moderate arsenic levels and incident cardiovascular disease. A prospective cohort study. *Ann. Intern. Med.* 2013; 159:649–59.
51. Nachman K.E. Ginsberge G.L., Miller M.D., Murray C.J., Nigra A.E., and Pendergrast C.B., 2017 Mitigating dietary arsenic exposure: Current status in the United States and recommendations for an improved path forward; *Sci Total Environ.* 2017 581-582: 221–236.
52. Navas-Acien A., Silbergeld E.K. Streeter R.A., Clark J.M. Burke T. A. And Guallar E., 2006 Arsenic Exposure and Type 2 Diabetes: A Systematic Review of the Experimental and Epidemiologic Evidence, *EPH* 114(5), 641-648
53. Navas-Acien A1, Silbergeld EK, Pastor-Barriuso R, Guallar E. Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA.* 2008 Aug 20;300(7):814-22
54. Navas-Acien, A., Umans, J.G., Howard, B.V., Goessler, W., Francesconi, K.A., Crainiceanu, C.M., Silbergeld, E.K., Guallar, E., 2009. Urine arsenic concentrations and species excretion patterns in American Indian communities over a 10-year period: the Strong Heart Study. *Environ. Health Perspect* *EPH.* 117, 1428–1433.
55. NRC (National Research Council) (2001) Arsenic in drinking water: update. National Academy Academies Press, Washington DC
56. NRC (National Research Council) (2014) Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic: Interim Report. National Academies Press
57. Pino A, Amato A, Alimonti A, Mattei D, Bocca B (2012). Human biomonitoring for metals in Italian urban adolescents: data from Latium Region. *Int J Hygiene Environ Health*, 215(2):185–90.
58. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (Text with EEA relevance)
59. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006, concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals, Official Journal No. L 396/1 of 30.12.2006 (hereinafter "REACH")
60. Saravanabhavan G., K. Werry K., M. Walker M., D. Haines D., M. Malowany M. and C. Khoury C., "Human biomonitoring reference values for metals and trace elements in blood and urine derived from the Canadian Health Measures Survey 2007–2013," *International Journal of Hygiene and Environmental Health*, vol. 220, no. 2, Part A, pp. 189-200, 2017.
61. Schoeters G, Den Hond E, Colles A, Loots I, Morrens B, Bruckers L et al. (2012a). The Flemish Environment and Health Study (FLEHS) – Second Survey (2007–2011): Establishing Reference Values for Biomarkers of Exposure in the Flemish Population. In: Knudsen E, Merlo DF, editors. *Biomarkers and human biomonitoring. Volume 1.* London: Royal Society of Chemistry, 135–165 (Issues in Toxicology, No.1).
62. Schulz C, Conrad A, Becker K, Kolossa-Gehring M, Seiwert M, Seifert B (2007b). Twenty years of the German Environmental Survey (GerES): Human biomonitoring – temporal and spatial (West Germany/East Germany) differences in population exposure. *Int J Hygiene Environ Health*, 210(3–4): 271–97.

63. Schulz C., M. Wilhelm, U. Heudorf and M. Kolossa-Gehring, "Update of the reference and HBM values derived by the German Human Biomonitoring Commission," *International Journal of Hygiene and Environmental Health*, vol. 215, no. 1, pp. 26-35, 2011.
64. Smith AH, Goycolea M, Haque R, Biggs ML. Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. *Am. J. Epidemiol.* 1998; 147:660–669.
65. Snoj Tratnik J, Mazej D, Horvat M (2012). Human biomonitoring studies in Slovenia –toxic metals, arsenic and essential elements. In: *Human Biomonitoring (HBM) – Linking Environment to Health and Supporting Policy. Proceedings of the Conference, Larnaca, Cyprus, 22–25 October 2012*. Nicosia: Ministry of Health, 88.
66. Thomas DJ., Li J., Waters SB., Xing W., Adair BM., Drobna Z., Devesa V. and Styblo M. Arsenic (+3 Oxidation State) Methyltransferase and the Methylation of Arsenicals. *Exp Biol Med* January 2007;232(1):3-13
67. Tremblay M., R. Langlois R., S. Bryan S., D. Eslinger D., J. Patterson J. Canadian health measures survey pre-test: design, methods, results *Health Rep.*, 18 (Suppl) (2007), pp. 21-30
68. Tseng C-H (2009) A review on environmental factors regulating arsenic methylation in humans. *Toxicol Appl Pharmacol* 235:338–350.
69. US FDA (U.S. Food and Drug Administration). Arsenic in Rice and Rice Products Risk Assessment Report. 2016. Available at <http://www.fda.gov/Food/FoodScienceResearch/RiskSafetyAssessment/default.htm>
70. Vahter M (1999) Methylation of inorganic arsenic in different mammalian species and population groups. *Sci Prog Lond* 82:69–88
71. Vahter M (2002) Mechanisms of arsenic biotransformation. *Toxicology* 181–182:211–217.
72. WHO. 2000. Air quality guidelines for Europe. WHO Regional Publications, European Series, No. 91. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf. January 26, 2015.
73. World Health Organization (WHO), "Human Biomonitoring - Facts and Figures," 2015.
74. Zheng LY, Umans JG, Tellez-Plaza M, Yeh F, Francesconi KA, Goessler W, Silbergeld EK, Guallar E, Howard BV, Weaver VM, Navas-Acien A. Urine arsenic and prevalent albuminuria: evidence from a population-based study. *Am. J. Kidney Dis.* 2013; 61:385–394.