Research Paper

Volume : 4 | Issue : 9 | Sept 2015 • ISSN No 2277 - 8179

Low Level Exposure to Arsenic in Drinking Water: A Review on Action Mechanism, Health Effects and Biomarkers.

Medical Science

KEYWORDS : Arsenic, water, low exposure, biomarkers.

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ABSTRACT

Arsenic has been recognized as a major public health issue worldwide. Chronic exposure at high levels (higher than 150µg/L) of this metalloid, ingested by means of food and drinking water, is a certain risk factor for a number of chronic diseases: cancer, cardiovascular diseases, peripheral neuropathy, diabetes and skin lesions. Although there is a plethora of studies published on this issue, in particular on environmental exposure at high levels, a lot is yet to be explained. The arsenic action mechanism and the existence of specific biomarkers to identify precociously the exposure, the effects and the genetic susceptibility are still matter of investigation. The purpose of this review is to shed light on this grey area, in particular focusing on the current knowledge about arsenic effects of exposure at low concentrations (lower than 150µg/L).

Occurrence

Arsenic is a metalloid commonly found as an environmental contaminant coming both from natural occurrence and from anthropogenic activity (Mandal and Suzuki, 2002), such as industry (ATSDR, 2011) and agriculture (WHO, 2011). Because of its ubiquity, the main sources of arsenic for humans are air, water, and food (ATSR, 2007).

The global burden of people exposed to Arsenic levels over the limit value of 10µg/L has been estimated to be around two hundred and twenty six million people (Murcott, 2012), with peaks of exposure in some world regions: Bangladesh, India, Taiwan, China, Mexico, Argentina, Chile and the USA and some European areas (Lucentini et al., 2013).

Metabolism

Although there are some suggestions of benefits coming from arsenic intake in some bacteria, a clear biological function has not yet been proven in humans (Smith et al., 1992).

However, arsenic belongs to the same group in the periodic table as phosphorus and they share many physicochemical properties (Hughes et al., 2011). For this reason, arsenic is considered the shadow element of phosphorus and it can potentially substitute it in a number of biochemical reactions (Dixon et al., 1997): energy storage as ATP, bone mineralization, cellular structural components (phospholipids, phosphoproteins, etc.), oxygen transport and acid base balance (Baker and Worthley, 2002).

Arsenic ingested by means of drinking water is absorbed in the gastrointestinal tract (Pomroy et al., 1980; Vahter, 2000) and then transported to different organs mainly bound to the SH protein domains and low-molecular-weight compounds such as glutathione (GSH) and cysteine (NRC, 1999; NRC, 2001). Arsenic is then methylated in the liver, through enzymatic and non-enzymatic processes, to a number of compounds: Monomethylarsonic acid (MMA^{V}), Dimethylarsinic acid (DMA^{V}), Monomethylarsonous acid (MMA^{III}) and Dimethylarsinous acid.

Arsenic ingested through drinking water is eliminated by urinary excretion. This includes trivalent, pentavalent and even methylated forms (Buchet et al., 1981).

Arsenic is also excreted in human milk, although at low levels (FAO&WHO, 2011). The biological half-life of inorganic arsenic is about 4 days, but is slightly shorter following exposure to arsenate rather than to arsenite (Pandey et al., 2007; Buchet et al., 1981).

Arsine is the most toxic form, followed by the arsenites [arsenic(III)] , the arsenates [arsenic(V)] and the organic arsenic compounds (WHO, 2011).

Arsenic's precise mechanism of action still remains unclear (Wu et al., 2013), but several pathways have been proposed. The majority of arsenic - related effects are due to its capability to induce oxidative stress through the formation of reactive oxygen species (ROS) and reactive nitrose species (RNS) (Jomova et al., 2011; Kitchin, 2001; Gebel , 2001; Bhattacharjee, 2013; Kitchin, 2010). Arsenic-induced ROS increases the expression of various pro-apoptotic molecules such as Bax and Bid, and consequently decreases the expression of anti-apoptotic molecules such as Bcl-2 and Bcl-XL. Simultaneously, ROS also provokes a calcium imbalance in cells and decreases the mitochondrial membrane potential, leading to opening of the membrane pore and to a consequent cytochrome c release from the mitochondria. This acts as a trigger of various pathways that end in a hyperactivation of caspase-dependent apoptosis. Besides the over cited pro-apoptotic effect, arsenic-induced oxidative stress is responsible for several effects: genotoxicity (Kitchin, 2001; Gebel, 2001), modified signal transduction (Kumagai and Sumi, 2007; Porter et al., 1999), abnormal cell proliferation and altered DNA repair (Andrew et al., 2006). Arsenic is not responsible for direct DNA damages but it behaves more like a co - mutagenic element because it enhances the mutagenic effect of UV radiations in mammalian cells (Li and Rossmann, 1991). Moreover, inorganic arsenic increases the expression of some growth factors like GM-CSF and TGF-α (Germolec et al., 1997; Germolec et al., 1998) and of the signaling protein Rac1, involved in regulating the cell cycle (Verma et al., 2002).

In the last years, even if with controversial evidence, a number

of studies have demonstrated that arsenic exposure is even associated with epigenetic effects through both hypo- and hypermethylation of DNA (Reichard and Puga, 2010).

Pathogenesis and health effects

In 2010, WHO and FAO, basing on the recent epidemiological evidences, have proposed a tolerable intake limit for arsenic at 3 μg/kg per day (FAO&WHO, 2011). High levels of arsenic exposure (> 300 μg/L) are clearly demonstrated to be an important risk factor for a number of human diseases. Chronic exposure is mainly associated with skin lesions, including hyperkeratosis, hyperpigmentation or hypopigmentation (Germolec et al., 1996; Mazumder et al., 1998; Rahman et al., 1999). Indeed, keratinocytes are the major target cells of arsenic toxicity (Liao, 2011) and it has been assessed that inorganic arsenic stimulate an over-expression of growth factors, i.e. GM-CSF and TGF-α (Li and Rossman, 2011; Germolec et al., 1997; Germolec et al., 1996), and of the signaling protein Rac1 (Germolec et al., 1998), which is mainly involved in regulating the cell cycle and in maintaining epidermal stem cells. Moreover, chronic exposure to arsenic and its compounds is significantly related to cardiovascular and peripheral vascular effects, including *blackfoot disease,* peripheral arterial disease, coronary heart disease, myocardial infarction, stroke (Navas-Acien et al., 2011) and hypertention (Abhyankar et al., 2012). This is mainly related to the production of reactive oxygen species (ROS) that enhance the expression of inflammatory mediators, cytokines and pro atherosclerotic genes, like HO-1 and MCP-1 (Barchowsky et al., 1999; Simeonova, 2004). In addition, arsenic is able to induce vasoconstriction and vasculopathies decreasing the activity of endothelial nitric oxide synthase (eNOS) (Tsou et al., 2005) and enhancing calcium sensitization in smooth muscle with consequent phosphorylation of myosin light chain kinase (MLCK) (Li et al., 2005). It is then likely that arsenic and its compounds are also responsible for an increased platelet aggregation with an enhancement of thrombus formation (Lee et al., 2002).

Arsenic and its compounds are able to induce immunotoxicological effects (Dangleben et al., 2013), neurotoxicity, in particular progressive peripheral neuropathy (Chakraborti et al., 2003), and diabetes type 2 (T2D) (Navas-Acien et al., 2006; Jovanovic et al., 2013). Concerning neurotoxicity, arsenic could act through different mechanisms: oxidative stress (Dwivedi and Flora, 2011), inflammation (Fry et al., 2007; Vega et al., 2001), endothelial cell dysfunction (Luo et al., 2009), neoangiogenesis (Meng et al., 2010) and increase of β amyloid levels (Dewji et al., 1995), hyperphosphorylation of tau protein (Vahidnia et al., 2007), inflammation, endothelial cell dysfunction (Lee et al., 2003) and neoangiogenesis (Meng et al., 2010).

In diabetes, chronic exposure to arsenic and its compounds induces both β-cell dysfunction and insulin resistance, through a mechanism of oxidative stress (Fu et al., 2010), which provokes a progressive β-cell failure, and a decreased the nuclear receptor PPAR-μ (*Peroxisome proliferator-activated receptor gamma*) (Yadav et al., 2013), involved in regulation of fatty acid storage and glucose metabolism, that may reduce the sensitivity of insulin responsible for insulin activation (Singh et al., 2011). At high doses, in case of acute intoxication, arsenic is even able to interfere with ATP-dependent insulin secretion and with glucose transporters (GLUTs) due to its ability to be the shadow element of phosphate (Tseng, 2004).

Arsenic-induced effects on health are much more evident in children. There is some evidence that chronic ingestion of arsenic-contaminated water interfere with their normal development, causing delayed growth, impaired immune function (Raqib et al., 2009; Soto-Pena et al., 2006) and neuro-behavioural deficits (Wasserman et al., 2004; Rudnai et al., 2014), although no conclusive results are available at the moment.

Furthermore, some epidemiological studies have suggested the existence of a statistical association between pregnant women's exposure to elevated arsenic concentrations in drinking water and increased risk of spontaneous abortion, stillbirth, pre-term birth, neonatal death, birth defects and low weight at birth (Milton et al., 2005; Hopenhayn-Rich et al., 2000; Rahman et al., 2009; Bloom et al., 2014)

In 2012 the International Agency for Research on Cancer (IARC) classified arsenic and its compounds in Group 1 (carcinogenic to humans). Indeed, epidemiological studies have observed that exposure to high levels of arsenic in drinking water is associated with an increased risk of bladder cancer (Saint-Jacques et al., 2014; Smith et al., 1998), of lung cancer (Smith et al., 1998), of skin cancer (Tseng, 1977) and of kidney (Smith et al., 1992), prostate and liver cancer (Yang et al., 2008; Chen et al., 1992). The increased risk of cancer is related mainly to inorganic arsenic (Chen et al., 1992), although studies on cellular and animal models have suggested methylated compounds might play a more dangerous role (Kojima et al., 2009). Recent studies seem to demonstrate that chronic exposure to arsenic and its compounds trigger the carcinogenesis process through both genotoxic effect and epigenetic deregulation (Bustaffa et al., 2014), inducing genome instability and deregulation of tumor suppressor genes and oncogenes (You and Jones, 2012).

Indeed, when arsenic enters the cell, it induces the production of reactive oxygen species (ROS) and reactive nitrose species (RNS): superoxide anion, hydroxyl radical, hydrogen peroxide, reactive nitrose species and arsenic-centered and arsenic peroxyl radicals (Wu et al., 2013; Gebel, 2001; Shi et al., 2004). Although their mechanism of action still remains unclear, it is very likely that these reactive species are the main cause of arsenic induced genomic instability through DNA damage, inefficient DNA repair, Telomere dysfunction, mitotic arrest, apoptosis and even epigenetic dysregulation (Bhattacharjee et al., 2013), in particular, through hypo- and hypermethylation of DNA (Zhao et al, 1997; Mass and Wang, 1997). Concerning international and national regulation, US Environmental Protection Agency in 2001 fixed a limit value for arsenic in drinking water at 10 μg/L; this was followed by the European Community in 2003 by the Drinking Water Directive 98/83/EC that replaced the previous accepted threshold of 50 μg/L.

If exposure to high concentrations of arsenic and its compounds is clearly demonstrated to be a risk factor for a number of human diseases, exposures to low-to- moderate levels of this metalloid (<150μg/L) still give substantially inconclusive results, because of difficult individual exposure assessment, of the limited sample size of the most part of the existing studies and because of their poor robustness (Chen et al., 2009).

An extensive review has been carried out through PubMed research engine to collect relevant studies, published till June 2015, concerning human exposure to arsenic concentrations lower than 150 μg/L by the mean of drinking water.

From the main evidences in scientific literature, chronic exposure to low-to-moderate levels of arsenic results to be strongly associated with skin lesions (Mazumder et al., 1998; Bustaffa et al., 2014), respiratory symptoms (Parvez et al., 2013) and cardiovascular diseases (Moon et al., 2013). A little less robust is the association between arsenic exposure and type 2 diabetes. Indeed, if most of scientific literature detects an increased risk (James et al., 2013; Moon et al., 2013), there is a number of studies with no conclusive results (Chen et al., 2010). Concerning neoplasms, instead, studies are substantially controversial.

Volume : 4 | Issue : 9 | Sept 2015 • ISSN No 2277 - 8179

Moreover, three main longitudinal studies have been carried out on low-to-moderate arsenic exposures: the Strong Heart study, the Health Effects of Arsenic Longitudinal Study (HEALS) and the National Health and Nutrition Examination Survey (NHANES).

The Strong Heart study is a longitudinal study, supported by the National Heart, Lung, and Blood Institute (NHLBI) since 1988, that aims to assess risk factors of cardiovascular diseases in native Americans. Concerning arsenic exposures to low-to-moderate levels, the study evidenced an increased risk for cardiovascular disease (Moon et al., 2013; García-Esquinas et al., 2013), type 2 diabetes (Moon et al., 2013; James et al., 2013) and lung, prostate, and pancreatic cancer (García-Esquinas et al., 2013).

Since 2008 the University of Chicago has coordinated the HEALS longitudinal study, that evaluated arsenic toxicity in more than 20.000 people exposed at low-moderate levels of arsenic (0.1 to 864 μg/L, mean 99 μg/L) in Araihazar, Bangladesh.

The results of this study suggested an increased risk of skin lesions, hypertension, neurological dysfunctions (Ahsan et al., 2006), respiratory symptoms (Parvez et al., 2013) and mortality for all causes (Ahsan et al., 2006).

The NHANES study, aimed to assess the health and nutritional status of adults and children in the United States, focused on the relationship between low-to-moderate arsenic exposures and type 2 diabetes, with no conclusive results (Bustaffa et al., 2014).

Biomarkers of exposure

The most commonly used biomarker is the measurement for total arsenic, but the US Centers for Disease Control and Prevention suggest that it would be preferable to determine seven different arsenic species: arsenobetaine (AB), arsenocholine (AC), trimethylarsine oxide (TMAO), Arsenate, Arsenite, MMAV and DMAV (Verdon et al., 2009). Biomarkers of exposure to arsenic and its compounds can be checked from urine, blood, hair and nails (Hughes, 2006). Blood and urine concentrations reflect acute exposures. Urine samples have the advantage of detecting chronic exposures, but they have deep variability in dilution because of the differences in the fluid intake by humans (Nermell et al., 2008).

Arsenic blood levels are not considered a reliable indicator of exposure (Pomroy et al., 1980) because arsenic is rapidly cleared from the blood. In chronic high exposures, however, arsenic in the blood reaches a steady state and, therefore, may well reflect the exposure (Hall et al., 2006).

Hair and nails allow to detect chronic exposure, happened in the preview 6-12 months for hair and fingernails samples (Fleckman, 1997) and in the last 2 years for toenails (Karagas et al., 2000; Mandal et al., 1998). Although total arsenic is the most commonly used biomarker, a plethora of other molecules has been investigated with good results in the last decade, as shown in Table 1. Blood and urinary porphyrins, urinary levels of delta-Ala in animal models, placental expression of the arsenic transporter AQP9, urinary concentration of α1-MG, the expression of GAL1, serum levels of Heat shock protein 70 and Glycophorin A are just some examples.

Moreover, precocious clinical manifestations such as skin hyperpigmentation and hyperkeratosis have been suggested to detect long term (>1 year) exposure.

Biomarkers of effect

A large number of biomarkers of effect have been reported in scientific literature, as shown in Table 2, but none of them is attributed specifically to arsenic (NRC, 2001).

The majority of studies have investigated levels of biomarkers of oxidative stress, like OHdG and N(7)-methylguanosine in subjects chronically exposed to arsenic and its compounds. Moreover, Micronuclei have frequently been examined as a possible biomarker of arsenic-induced DNA damage; the focus has been on counting the Micronuclei in the peripheral blood lymphocytes, the oral mucosa cells and the urotherial and bladder cells. However, genotoxicity is not the only target that has been evaluated; growth factors (i.e. EGFR and TGF-α, oncogenes (i.e. PTTG1) and various tumor suppressor genes (i.e. HBD-1 and p53) have been investigated as well, although with no univocity of results. Furthermore, in recent years, non-specific indicators have also been investigated, such as high pulse pressure, increased carotid artery intima-medial thickness, proteinuria and serum level of Clara cell proteins; but these investigations have not provided satisfactory results.

Genomic Biomarkers of susceptibility

Susceptibility to the toxicity of arsenic and its compounds seems to present inter-individual variability. Observational studies suggest that subjects who metabolize arsenic efficiently are at lower risk for toxicities such as arsenical skin lesions. These differences are probably due to a genetic variability in the enzymes involved in arsenic metabolism and detoxification (i.e. arsenic III methyltransferase and gluthatione S-transferase), or are involved in cellular transport (i.e. SLCO1B1). Single nucleotide polymorphisms (SNPs) in these genes could play a role in the arsenic exposure and availability. There is also evidence of the interaction between gene polymorphisms and arsenic exposure in the susceptibility to certain diseases, such as diabetes, skin lesions, atherosclerosis, etc. A great effort has been made to characterize the genetic basis of arsenic metabolism since there is considerable inter-individual variation in urinary arsenic metabolism . To date there is evidence that the SNPs in the glutathione s-transferase gene GSTT1 are involved in arsenic metabolism and can influence the internal dose of methylated arsenic (Kile et al., 2013). A study of the Taiwanese population reported that subjects carrying the GSTT1 null genotype had an elevated percentage of DMA in their urine (Chiou et al., 1997). Furthermore, other studies have reported an increased risk of developing bladder cancer and arsenic-induced skin diseases in subjects carrying the GSTT1 null genotype (McCarty et al., 2007; Chung et al., 2013). Several studies have investigated the possible involvement of polymorphisms in other GST genes, such as GSTM1 and GSTO, but with inconsistent results (Beebe-Dimmer et al., 2012; Rodrigues et al., 2012).

The role of GSTO in arsenic metabolism seems limited to reduction of pentavalent arsenicals and has only been demonstrated in vitro. Another key enzyme in the metabolism of arsenic is the AS3M (arsenic methyltransferase). Genetic variations in AS3MT have been associated with changes in arsenic biotransformation (Hernández et al., 2008), with altered cognitive function (Edwards et al., 2014) and with skin pathologies related to exposure to arsenic (Valenzuela et al., 2009). AS3MT polymorphisms are associated with changes in urinary percentage of MMA, and increased MMA concentration maybe associated with increased susceptibility to arsenic-related health effects (Antonelli et al., 2014). In 2014 Hernandez et al described an association between AS3M variants and the frequency of micronuclei, that are markers of genotoxicity of arsenic. An interaction between well-water arsenic (≥ 40.4 μg/L) and GG genotype of AS3MT rs3740392 in relation to carotid artery intima-media thickness has also been described (Wu et al., 2014).

Variations within NOTCH2 gene have been reported to increase the susceptibility to arsenic-induced T2DM. In particular, the C allele of rs699780 SNP, located in this gene, significantly

increased the susceptibility to T2DM among people exposed to arsenic (Pan et al., 2013). NOTCH2 is generally involved in the development and cell fate decision, and there is increasing evidence that the NOTCH2 signaling is also important for immune functions. Another gene, NALP2, involved in host defense and inflammation, has been studied in relation to arsenic-induced skin diseases. NALP2 is a major component of the inflammasome complexes, which are multiprotein complexes in cytoplasm playing a vital role in maturation of the proinflammatory cytokines (Martinon et al., 2007. A lot of NALP-inflammasomes are associated with diseases and pathologies by alteration of cytokine levels consequently resulting in development of various hereditary autoinflammatory syndromes (Church et al., 2006). Interestingly, it is shown that the minor allele of the A1052E SNP significantly decreased the risk of developing arsenic-induced skin lesions (Bhattacharjee et al., 2013). Also the NRF2 nuclear factor erythroid 2-related factor (NRF2) has been proposed as being involved in the risk of skin lesions in people exposed to arsenic-contaminated water, but with negative results (Cordova et al., 2013). The NRF2 transcription factor regulates the expression of several genes involved in Arsenic detoxification, such as GST and several multidrug-resistant proteins. Polymorphisms located at the promoter region of NRF2 may influence ROS-related diseases by altering the expression of its mRNA(Cordova et al., 2013). Recently, two NRF2 SNPs were investigated in relation to cellular sensitivity to As-mediated effects. In particular the authors studied the levels of NFE2L2 mRNA and its target gene NQO1, at basal level and after As exposure, in lymphoblastoid cells carrying the different genotypes of these SNPs. The study, however, did not show statistically significant results (Morales-Marin et al., 2015). Recently, common variants in the SLCO1B1 gene, that codes for an organic anion transporter, were associated with differences in arsenic metabolites; the minor allele of rs1564370 and rs2291075 were associated with lower MMA and higher DMA (Gribble et al., 2013).

In conclusion several evidences suggest that the occurrence of polymorphisms in genes associated with Arsenic metabolism and detoxification may contribute to the individual variability in arsenic-related disorders risk. Although epidemiological studies have provided a link between the inter-individual variability and the susceptibility to arsenic toxicity, there is much to understand regarding the health impact and further studies are necessary to develop specific preventing strategies and/or therapeutic strategies for the arsenic-related disorders. The identification and validation of genomic biomarkers could help to better understand the mechanisms of action and dose-response relationships for arsenic exposure and human health risk. The study of the genetic variability will be able to provide important mechanistic insights into the pathogenesis of disease processes and reduce the time gap exposure and recognition of disease-relevant effects, allowing to develop new and more effective strategies to reduce risk, such as exposure monitoring, health surveillance and individual risk characterization.

Prevention

Because there is no effective *treatment* of chronic *arsenic* poisoning at the moment, the great majority of international efforts must be focused on prevention and promotion strategies, in particular in those areas with high levels of arsenic contamination. Arsenic exposure mainly occurs through naturally contaminated groundwater. Therefore, primary prevention should be made first using alternative sources of water with lower levels of arsenic, including dug wells and surface ponds (ATSDR, 2011), or removing the metalloid from contaminated water. Secondly, it's fundamental for a successful intervention to inform people living in contaminated area on the arsenic-related risk and on the basic measures to carry out, in order to minimize the exposure. In particular, population should be educated to distinguish between arsenic free water -such as water containing less than 10 μg//l- and arsenic water over the recommended threshold. The first one should be used to drink and the second for all the other purposes, for example to cook and to wash (Singh et al., 2007). All these strategies acquire more and more importance because many international studies have confirmed that an elevated risk persists for decades after stopping the chronic exposure to high concentration of arsenic and its compounds (Argos et al., 2012). Though no effective treatment is available at the moment, except for the use of chelating agents like the antidote British anti-leusite (BAL) (Singh et al., 2007), the HEALS study has pointed out that arsenic-related risk is in a certain way modifiable by nutritional factors (supplements of folate, B group vitamins B, selenium, calcium, iron, zinc and antioxidants), life style factors (body mass index, cigarette smoking) and genetic determinants (Chen et al., 2009).

Conclusions and future perspectives

Exposure to Arsenic and its compounds by the mean of drinking water has been largely demonstrated to be an important risk factor for a number of acute and chronic diseases in human beings, although mainly at high levels of exposure (>150 μg/l). In spite of the plethora of scientific literature that has been produced in the last decades, at low levels (10-150 μg/l) the results remain substantially controversial, even if few recent studies open important perspectives to the association with the same pathologies involved in exposure to high levels of arsenic. This scarceness of certainties paves the way for further investigations and new research pathways. Indeed, if arsenic toxicity, also at low levels of exposure, was confirmed, this would expand target population to two hundred and twenty six million people worldwide, including arsenic coming both from geological and anthropogenic sources in water and food. Moreover, in absence of an effective therapy against acute and chronic intoxication, it's fundamental to put attention on lifestyle, nutrition and other individual factors, such as genetic susceptibility. Indeed, according to recent studies, these seem to be able to modulate arsenic toxicity, although without erasing it entirely, also after decades from initial exposure. But a lot is yet to be explained on the action mechanism of arsenic: none of the hypotheses have proven to be conclusive at the moment; the only certainty is that this metalloid plays its role through a complex series of different pathways. Irrespective to high or low levels of exposure, arsenic seems to trigger an effect of oxidative stress that is involved in all the arsenic-related diseases. Indeed, the production of oxygen reactive species (ROS) is the main responsible for arsenic induced genomic instability. ROS are able to induce DNA damage, inefficient DNA repair, telomere dysfunction, mitotic arrest, apoptosis and even epigenetic dysregulation, through both hypo- and hypermethylation of DNA. Therefore, a relevant contribution could certainly come from research pathways oriented towards three main tasks: to study the effects of exposure to low levels (≤150 μg/L) of arsenic, to completely disclose the pathogenic mechanism of this metalloid, and to identify specific biomarkers of exposure, effect and susceptibility to arsenic and its compounds. At the moment, a tough association between arsenic-related diseases and specific biomarkers, in particular of effect and susceptibility, hasn't been identified yet. Biomarkers represent the main future perspective of research on arsenic, particularly in a Public Health approach: they could permit to identify people more at risk of developing arsenic-related diseases, as well as to precociously point out the main targets for preventive actions.

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