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Professional paper

ARSENIC: EXPOSURE THROUGH THE FOOD CHAIN, TOXICITY, AND TOXICITY REDUCTION BY NUTRITIONAL COMPOUNDS

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Abstract

Arsenic is widely distributed in the environment, including water, soil, and rocks. Arsenic enters the food chain through food contaminated by arsenic pesticides, crops irrigated with arsenic-contaminated water, or crops grown in arsenic-rich soil. Among foods of plant origin, the highest concentrations of arsenic are found in rice, root and leafy vegetables. Arsenic can also be present in foods of animal origin, such as meat, fish, eggs, milk, and dairy products, as a result of animal exposure to arsenic through feed and drinking water. Arsenic causes acute and chronic toxicity through disruption of mitochondrial function and oxidative stress. Chronic exposure to arsenic leads to multisystem disease, neurotoxicity, hepatotoxicity, nephrotoxicity, carcinogenicity, and genotoxicity. The health risk in case of chronic exposure to arsenic is estimated according to the calculation of: PTWI (Provisional Tolerable Weekly Intake), ER (Exposure rate), HQ (Hazard Quotient), and AELCR (Annual excess lifetime cancer risk). It is of great importance to reduce the intake of arsenic in the population by monitoring important monitoring points, continuous analysis of food and drinking water, early diagnosis and intervention. Foods with a high content of antioxidants and bioactive compounds can reduce the toxic effect of arsenic. The most powerful medicinal plants for treating arsenic toxicity are garlic, turmeric, milk thistle, some dietary fibers, algae, green and black tea.

Keywords: arsenic, food, health risk, antioxidants

1. Introduction

Arsenic (As) is a chemical element, a metalloid that is widely distributed in the environment, including water, soil, and rocks. Arsenic is part of organic and inorganic compounds. Arsenic poisoning is a global health problem that affects millions of people worldwide through exposure from the environment, occupational activities, as well as intentional suicide and homicide attempts. The primary source of toxicity for the general population is contaminated water and food (Olsen & Morland, 2004; Kuivenhoven & Mason, 2022; Sofilic & Makic, 2019). Poisoning can occur by ingestion, inhalation and dermal absorption. Elemental arsenic is the least toxic. Arsenic compounds are very toxic, for example arsine is a very poisonous gas that is often obtained when working with raw materials which contain arsenic. Arsenic (III) oxide As2O3 is a white powder, odorless, with a sweet taste, poorly soluble in water, a strong poison which is used to obtain other arsenic compounds. It is used in medicine, industry for obtaining paints and varnishes, preserving wood and leather, etc. (Sofilic & Makic, 2019; Sarkanj et al, 2010).

Arsenic compounds are classified of trivalent and pentavalent (according to their chemical structure), of inorganic, and organic, of solid, liquid, and gaseous states. Inorganic arsenic compounds are highly toxic to all living cells, while organic arsenic compounds such as arsenobetaine and arsenocholine are well tolerated by living organisms and are less toxic to humans (Kuivenhoven & Mason, 2022).

2. Sources of arsenic

People can come into contact with arsenic through water from wells located in arsenic-rich soil layers or from water contaminated with industrial or agrochemical waste. They may eat food contaminated by arsenic pesticides, crops irrigated with arsenic-contaminated water, or crops grown in arsenic-rich soil. Dermal absorption of trivalent arsenic can also occur because it is more soluble in lipids compared to pentavalent arsenic. Arsinegas exposure is also a hazard, especially for occupationally exposed people because arsine is a colorless, odorless, tasteless, and non-irritating gas that causes serious health problems (Kuivenhoven & Mason, 2022; Mohammed *et al,* 2020).

Inorganic species of arsenic can often found at high levels in drinking water if groundwater comes into contact with soil containing elevated concentrations of arsenic. Increased concentration of arsenic in drinking water have been observed in several countries, including Chile, Bangladesh, India, China, Taiwan, USA, etc. Cases of industrial pollution of water and soil, as well as increased concentrations due to the past use of arsenic-based pesticides, have also been documented. Foods with a high content of inorganic arsenic are mostly of plant origin, particularly cereals, with rice having especially high concentrations. High levels of arsenic may occur as a result of an industrial accident during the food production process. Fish, shellfish, and seaweed generally have organic types of arsenic, arsenobetaine being the most common. Cereals are the major contributors to the consumption to inorganic arsenic through food. (Sarkanj *et al*, 2010; Nurchi *et al,* 2020; Genchi *et al*, 2022; Ghosh *et al,* 2019).

3. Arsenic toxicity

Acute poisoning tipicaly occurs due to accidental consumption of insecticides or pesticides. Ingestion of arsenic less than 5mg generally causes vomiting and diarrhea, which typically resolve within 12 hours. A lethal dose of arsenic ranges from 1 to 2 mg (As) per kg of body weight, and death can occur within one to four days. The acute toxicity of arsenic compounds with oxidation state +3 (organic and inorganic) is higher compared to compounds that are in oxidation stat e +5 (Olsen & Morland, 2004).

Long-term exposure to arsenic leads to a multisystem disease, with malignancy being its most severe consequence. The clinical features of arsenic toxicity can vary among individuals, population groups, and geographic areas. It remains unclear which factors determine the appearance of a specific clinical manifestation and which organs are most susceptible to chronic exposure to arsenic. A wide variety of clinical features are common in humans exposed to chronic arsenic toxicity. The beginning of the poisoning is insidious, with non-specific symptoms such as abdominal pain, diarrhea, and a sore throat, therefore, the correct diagnosis is often made later. The source of arsenic exposure has been identified in less than 50% of cases (Kapaj *et al,* 2006; Ratnaike, 2003; Saha, 1999).

Arsenic exposure disrupts mitochondrial function and inhibits mitochondrial respiration, affecting membrane potential and reducing ATP levels. Arsenic inhibits the mitochondrial NADH ubiquinone oxidoreductase, succinate dehydrogenase, and cytochrome C oxidase complexes, followed by increased production of reactive oxygen species, lipid peroxidation, and damage proteins and DNA (Parakash *et al,* 2015).

Chronic exposure to arsenic results in various cutaneous changes. Dermatological changes are common, and initial diagnosis often relies on identifying hyperpigmentation, diffuse melanosis, spotted melanosis, leukomelanosis, dyschromia, mucosal pigmentation, and keratosis. Arsenic may also contribute to the development of basal cell carcinoma in non-melanin-pigmented skin (Rajiv *et al,* 2022).

Neuronal damage as a result of heavy metal exposure is well documented. Epidemiological and experimental data indicate that arsenic exposure is a significant risk factor for many neurological diseases (Wang *et al,* 2012; Fatoki & Badmus, 2022). The mechanisms of arsenic-induced neurotoxicity are constantly evolving and very complex. The most studied mechanisms of arsenic-induced neurodegeneration involve oxidative

stress, mitochondrial dysfunction, and inflammation (Medda *et al,* 2020; Fatoki *et al,* 2019; Nino *et al,* 2017). Arsenic also negatively affects cognitive functions, intellectual abilities, and mental health. Previous studies conducted in various parts of the world such as Taiwan, India, Mexico, and Bangladesh, have shown that even at doses below 10 µg/L, chronic exposure of children to arsenic causes a significant decreases IQ and memory (Rahman *et al,* 2021; Tolins *et al,* 2014; Calderon *et al,* 2001).
Many studies of humans exposed to inorganic arsenic through oral route have observed signs of liver damage. Individuals exposed to lower concentrations of arsenic over extended period show increased liver enzymes in blood analysis, and histological examination reveal consistent findings of fibrosis, hepatocellular damage, inflammation, and hepatocellular carcinoma (Gaim *et al,* 2015; Das *et al,* 2012).
Similarly, the kidneys accumulate arsenic during chronic exposure to the element. The kidneys are the main route of arsenic excretion, as well as the main site of conversion of pentavalent arsenic to the more toxic and less soluble trivalent arsenic. Under the influence of arsenic, the capillaries, tubules, and glomeruli of the kidneys are damaged, which leads to chronic kidney disease (Prakash & Verma, 2021; Robles-Osorio *et al,* 2015; Saha *et al,* 1999).
Arsenic is a known human carcinogen with sufficient evidence of its carcinogenic risk. The biotransformation of arsenic from as(V) to As (III) and its methylated conjugates plays a key role in arsenic carcinogenicity at both genetic and epigenetic levels. Genetic changes primarily occur through the induction of reactive oxygen species during the biotransformation process (Hubaux *et al,* 2013). Arsenic exposure showed genotoxic properties in primary human lung epithelial cells,leading to chromosome damage and DNA double-stand breaks that initiate tumor formation.. Increased levels of reactive oxygen species as a result of arsenic exposure induce angiogenesis, which further contributes to tumor growth (Wei *et al,* 2019; Faita *et al,* 2013).

4. Presence of arsenic in food and water

In 2009, the Scientific Panel on Contaminants in the Food Chain, of the European Food Safety Authority EFSA adopted an opinion on arsenic in food. In this opinion, the EFSA panel concluded that the provisional tolerable weekly intake of 15 µg/kg body weight established by the Join FAO/WHO Expert Committee on Food Additives was no longer appropriate. as data had shown that inorganic arsenic causes lung, bladder, and skin cancer and other consequences in less than those levels. The Contamination Panel identified a range of benchmark dose lower confidence limit values between 0.3 to 8 µg/kg body weight per day for cancers of the lung, skin and bladder, as well as skin lesions (Commission Regulation (EU), 2023/465).
The human diet comprises cereals, legumes, vegetables, fruits and animal foods, all of which can contribute to the total intake of arsenic in humans. Despite the widespread presence of arsenic in various foods, only a few studies have quantified total arsenic intake. The EFSA Panel on Contaminants in the Food Chain quantified arsenic exposure from food and water in 19 European countries, with levels ranging from 0.13 to 0.56 µg/kg body weight per day for average consumers. Dietary arsenic exposure levels per kilogram of body weight were 2–3 times higher in children under 3 years of age than in adults (Sarkar *et al*. 2022; EFSA, 2009).

4.1. Arsenic in drinking water: According to EU Regulations and the Drinking Water Safety Regulation of R. S. Macedonia, total arsenic content in drinking water should not exceed 10 µg/kg for tap water and natural mineral drinking water (EU Regulation, 2023; Rulebook, No. 183, 2018). Most cases of relatively high levels of arsenic in drinking water have been reported in South Asian countries like India, Bangladesh, and Cambodia (Uppal *et al.* 2019), countries from all continents, including Europe. High levels of arsenic in drinking water have been observed across Europe, mostly in areas where complex biogeochemical interactions mobilize arsenic from volcanic rocks and sulfide mineral sediments into groundwater (Herath *et* *al.* 2016). Some examples include average arsenic values ranging between 7.7 and 28 µg/kg in drinking water in various Central European countries, especially in Hungary. Arsenic levels ranged from < 0.5 to 240 µg/kg in groundwater of the Pannonian basin and maximum arsenic levels up to 233 µg/kg in natural water supplies in Great Britain (Cubadda *et al.* 2015; Lindberg *et al.* 2006; Rowland *et al.* 2011; Middleton et al. 2016). In these areas, due to relatively high levels of arsenic in drinking water, consideration should be given to arsenic intake through locally produced food (e.g. bread, vegetables etc.) which also contains higher levels of arsenic (Cubadda *et al.* 2015).

*4.2. Arsenic in food of plant origin***:** In 2014, in the scientific report on dietary exposure to inorganic arsenic in the European population, EFSA identified cereal products, rice, milk and dairy products as the main contributors to arsenic exposure. Different types of rice and rice-based products such as rice cakes, waffles, crackers, and rice flakes contain relatively high levels of inorganic arsenic. Relatively high levels of arsenic have been found in rice-containing products for infants and young children (Signes-Pastor *et al.* 2016; Gu *et al*. 2020; EFSA, 2014). Among various cereal crops, it is well-known that rice plants accumulate more inorganic arsenic than similar cereal crops due to their ability to transfer arsenic into the grain. Cereal-based products that did not contain rice generally show lower levels of inorganic arsenic compared to those contain rice. Arsenic concentrations in rice can vary widely depending on the growing region (Arcella *et al.* 2021). A high concentration of inorganic arsenic in rice has been reported in several countries: < 100 µg/kg in India, 130 µg/kg in Bangladesh, 140 µg/kg in Taiwan and China, and 190 µg/kg in Japan (Upadhyay *et al.* 2019). There is a positive correlation between the presence of arsenic in soil and wheat grains, milling the wheat significantly reducing the presence of arsenic in white flour compared to wholemeal flour and bran (Zhao *et al.* 2010). In cereals such as wheat, corn, and barley, the grains generally have the lowest concentration of arsenic compared to other parts of the plant (Bianucci *et al.* 2020). Legumes such as beans, peas, lentils, soybeans, and peanuts have lower levels of arsenic in the grains compared to other plant parts,although, if contamination in soil and irrigation water is very high, arsenic concentrations can also increase in grains (Bianucci *et al*. 2020; Jinadasa & Edrisinghe, 2019).

Fruits and vegetables can accumulate arsenic in the edible and non-edible parts of the plants. Excessive accumulation in edible parts can have negative effects on human health. The concentration of arsenic in fruits is lower than in vegetables. Leafy and root vegetables have shown higher levels of arsenic, indicating that arsenic accumulates more in the roots and leaf tissues of plants. Among root vegetables such as potatoes, carrots, and swede, unpeeled products showed significantly higher arsenic content compared to peeled products. In apples, beets, zucchini, cucumbers, parsnips, and pumpkins, there was no significant difference in the total arsenic concentration between the unpeeled and peeled products. High concentrations of arsenic have been found in lettuce. Tomatoes have shown low arsenic accumulation when grown on arsenic-containing soil (Meharg *et al.* 2012; McBrige, 2013). Numerous studies on the presence of arsenic in fruits and vegetables grown in polluted regions showed a higher concentration of arsenic than the maximum permissible limits according to FAO/WHO, which is 0.1 mg/kg of fresh fruits and vegetables (FAO/WHO, 2015; Ezeilo *et al.* 2020; Khan *et al.* 2018).

4.3. Arsenic in food of animal origin: Milk in certain parts of the world is contaminated with arsenic. Arsenic has been found in breast milk and animal milk as a result of the ingestion of contaminated water and food. Thus, the concentration of arsenic in milk can be high and cause toxicity in humans. Contamination can also come from milk handling equipment, storage methods, packaging, and animal housing. When cows, goats, and sheep are exposed to high concentrations of arsenic, it will also be present in their milk. Drinking water is one of the main causes of arsenic contamination in livestock, since the daily water intake of animals can be up to 75L, arsenic can accumulate in animals and be excreted in milk. Arsenic is also found in dairy products such as yogurt, cheese, milk powder, etc. (Perez Carrera & Fernandez Cirelli, 2005; Hameed *et al.* 2019; Van

Chuen *et al*. 2022).A positive association has been established between arsenic levels in animal feed and arsenic concentrations in various sections of meat. In chicken meat, there is a higher concentration of arsenic in the liver and internal organs, in other parts, there are lower concentrations of arsenic (Idrees & Hussain, 2022). Although higher concentrations of arsenic can be found in poultry, arsenic exhibits a low biological ability to transfer from the body to the egg, and very low levels of arsenic have been found in eggs (Ghosh *et al.* 2012). In pork that was obtained from animals fed with food containing arsenic, mostly rice bran, arsenic accumulates mostly in the hair, less in the liver and kidneys, while the presence of arsenic was not detected in the muscle tissue. Arsenic is quickly eliminated from the pig's body through feces and urine, making the pork safe for human consumption (Liao *et al.* 2020; Scollo, 2022). Arsenic has also been found in beef, lamb, and goat meat, in muscle, liver, and kidney (Yakup *et al.* 2018; Khalid *et al.* 2018).Continuous exposure of fish to low arsenic concentrations causes bioaccumulation, particularly in the liver and kidneys, resulting in disrupted metabolism. Lower concentrations of arsenic have also been found in fish muscle tissue (Kumari *et al.* 2016; Dwivedi & Singh, 2021).

5. Reducing arsenic intake through the food chain

It is very important to reduce the presence of arsenic in the food chain. Table 1 shows monitoring points and interventions to reduce arsenic in food in different parts of the food chain in order to reduce the dietary exposure of the population (adapted from Nachman *et al.* 2018).

Table 1. Opportunities for monitoring and intervention of arsenic exposure in the food chain (adapted from Nachman *et al.* 2018).

Supply chain phase	**Agronomic & production**	**Processing**	**Education**	**Preparation & consumption**	**Biological exposure markers**
Examples of monitoring and/or intervention opportunities	Low arsenic – accumulating cultivar selection Irrigation water quality testing Low arsenic fertilizer sourcing Soil testing	Ingredient monitoring and substitution Removal of high-arsenic containing commodities	Modification of consumer preferences Risk communication Social media Targeting vulnerable populations	Modification of consumption patterns Modification of cooking techniques Monitoring dietary patterns	Monitoring exposure through blood and urine analysis Monitoring vulnerable populations

As important monitoring points that should be monitored are soil, irrigation water, animal feed, and raw materials in the food industry, secondary contamination should be prevented through the production process, packaging, and storage. It is of great importance to monitor the vulnerable population and arsenic exposure in the population through blood and urine analysis. Biomarkers that indicate arsenic intake in the body are: increased hepatic enzymes AST and ALT, elevated levels of creatine and urea in blood plasma and total arsenic and its metabolites in urine (Nachman *et al.* 2018; Gaim *et al.* 2015; Fatoki *et al*. 2019; Mohammed *et al.* 2020; Middleton *et al.* 2016).

It is very significant to reduce the exposure to arsenic through rice, a food that has the highest potential for arsenic absorption in grains. The best possibilities for reducing the intake of inorganic arsenic through rice are the use of rice varieties with restricted uptake and transport of arsenic to the grains, control of irrigation water, rice cultivation in geographical areas with low arsenic content in the soil, optimization of the cooking of rice, washing the grains well before cooking, using more water to facilitate the migration of arsenic from the grains into the water, and removing the water after cooking. There is a need to limit the consumption of whole grains of rice, especially for populations with high rice intake (Munera *et al.* 2015).

6. Population health risk assessment

The health risk of chronic exposure to arsenic is estimated according to the calculation of certain formulas. Provisional Tolerable Weekly Intake PTWI is calculated according to the following equation:

$$PTWI = \frac{C\ x\ WC}{BW} \tag{1}$$

C - concentration of metals in food (mg/kg)
WC - average consumption per week (kg/week)
BW - average body weight (kg)

ER (Exposure rate) is calculated with the following equation:

$$ER = \frac{C\ x\ IR\ x\ ED}{BW\ x\ AT} \tag{2}$$

C – concentration of metals in food (mg/kg)
IR – amount of consumed food (kg/year)
ED – period of time in contact with the metal (year)
BW – average body weight (kg)
AT - average time or period of exposure (day)

HQ (Hazard Quotient) is calculated according to the following equation:

$$HQ = \frac{ADD}{RfD} \tag{3}$$

ADD - average daily dose (mg/kg.day)
RfD – reference dose for As (3 x 10-4 mg/kg.day)

If HQ is ≥ 1, then there is a potential health risk, and it is necessary to intervene and take protective measures. If HQ < 1, then there is no major health risk.
Cancer risk is calculated according to the following equation:

$$AELCR = \frac{Exposure\ rate\ x\ SF}{DL\ x\ 365} \tag{4}$$

AELCR - Annual excess lifetime cancer risk
SF – cancer slope factor, for As is 1,5 mg/kg, day
DL – average human longevity
The lowest acceptable limit is 1 x 10-4 (Edirisinghe & Jinadasa, 2019).

7. Natural nutritional compounds for the treatment of arsenic toxicity

More than 200 million people worldwide are currently exposed to the chronic effects of arsenic. Due to the extensive damage to various body organs caused by arsenic, investigations of therapeutic methods for its treatment are very current and important. Measures focusing on reducing arsenic toxicity, early diagnosis, and therapy for arsenic-induced diseases are urgently needed (Susan et al. 2019; Bjorklund et al. 2022). Chelator therapy is the most widely used method for the treatment of arsenosis, but it is associated with hepatotoxicity, neurotoxicity, blood abnormalities, and other adverse effects. Therefore, it is very important to reduce toxicity in a natural way. Phytopreparates and other natural products can effectively reduce arsenic-induced toxicity (Susan et al. 2018; Bjorklund et al. 2022). Because arsenic affects intracellular antioxidant processes, exogenous antioxidant supplementation may reduce arsenic-induced pro-oxidative processes. Antioxidants are also recommended as a symptomatic treatment because the metabolism of arsenic in the body can increase the generation of free radicals and cause oxidative stress. Diet is very important in preventing arsenic-related disorders. Low dietary protein and micronutrient intake increases susceptibility to arsenic-related diseases because a nutritional deficiency results in the slow removal of arsenic from the body. Properly selected food and nutrition can positively affect metabolism and reduce the toxic effects of arsenic (Yu et al. 2016). Vitamins (A, C, and E), polyphenols, and curcumin regulate the activity of glutathione and antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase), they have a protective role against oxidative stress caused by arsenic. The high content of hydrophilic phenolic compounds from herbal extracts in teas may provide significant antioxidant effects. For example, polyphenols from green and black tea significantly reduce arsenic-induced toxicity in experimental animals. Exogenous antioxidants, such as the trace elements zinc and selenium, are also very useful for arsenic detoxification (Mehrandish et al. 2019; Yu et al. 2016; Raihan et al. 2009, Rahman et al. 2019).

The most powerful natural sources for treating arsenic toxicity are garlic, turmeric, milk thistle, some plant fibers, and algae. Vegetables that contain organosulfur compounds, such as cabbage, broccoli, cauliflower, swede, and garlic, are useful for clearing arsenic from the liver. The naturally occurring organosulfur compound diallyl sulfide found in garlic reduces mitochondrial toxicity from arsenic. Modified citrus pectin showed a significant increase of about 130% in urinary arsenic excretion. Apple peel extract, which is rich in polyphenols, milk thistle flavonolignans, and silibinin, reduces toxicity through antioxidant activity. Spirulina extract can remove arsenic from isolated liver tissues. Clinical trials of patients with arsenosis in Bangladesh have shown the benefit of antioxidants such as vitamins A, C, and E (Das & Chaudhuri, 2014; Khandker et al. 2006; Bjorklund et al. 2022).

There is no specific therapy for chronic arsenic exposure resulting from long-term ingestion of contaminated food and water, so it is very important to reduce arsenic intake. Diet can affect the bioavailability, metabolism, and toxicity of arsenic. Lack of micronutrients in food can lead to more pronounced arsenic toxicity (Bjorklund et al. 2022).

8. Conclusion

Arsenic is a concerning element for both the environment and human health. It exists in organic and inorganic compounds, with inorganic forms being highly toxic to all living cells, while organic forms are better tolerated by organisms and less toxic to humans. Arsenic poisoning can occur through ingestion, inhalation, or dermal absorption.

Chronic arsenic exposure leads to a range of diseases, with common manifestations including dermatological changes like hyperpigmentation, diffuse melanosis, spotted melanosis, leukomelanosis, dyschromia, mucosal pigmentation, and keratosis. Additionally, chronic arsenic exposure can result in neurotoxicity, hepatotoxicity, nephrotoxicity, carcinogenicity, genotoxicity, and other adverse effects.

Arsenic exposure via food can occur through various pathways, including drinking and cooking water, cereals, fruits, and vegetables cultivated in arsenic-contaminated soil or irrigated with arsenic-contaminated water, as well as animal products. To mitigate arsenic exposure, it is crucial to control the presence of arsenic in food, feed, drinking water, and soil. Regular monitoring of arsenic exposure in the population through blood and urine analyses is essential.
A diet rich in natural antioxidants can help reduce arsenic toxicity. Some of the most potent natural sources for mitigating arsenic toxicity include garlic, turmeric, milk thistle, certain plant fibers, seaweed, and green and black tea.

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