Arsenic-Dietary Sources and Metabolism

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Abstract

Arsenic has long been an environmental agent and element of concern regarding human health. It is implicated in the development of cancers including skin and bladder. Arsenic also causes a number of dermatological problems, affects the vascular system, and is thought to negatively impact neurodevelopment. The primary sources of exposure worldwide are through drinking water and food. Arsenic is also found in several chemical forms which has relevance for toxicological expectations. Arsenic is found primarily in grain and cereal crops, especially rice as well as certain fruits and vegetables. For some widely consumed staple root crops consumed in South America and elsewhere including cassava, potato, and sweet potato, concentrations of arsenic in the edible portions are generally low and below those of health concern. However, diet is likely important in the metabolism and toxicokinetics of arsenic. Arsenic is metabolized through a series of methylation and reduction reactions which facilitate its detoxification and excretion. Methylation is highly dependent on adequate one carbon metabolism which generates the methyl donors. Folate sufficiency likely plays a prominent role in arsenic toxicity and susceptibility. In conclusion, diet is a major contributor to both arsenic exposure and arsenic elimination.

Brief Overview of Arsenic

Arsenic is arguably one of the oldest known environmental toxins that is not of biological origin. Arsenic has been used since ancient times as both a treatment and a poison being considered the “poison of kings and the king of poisons”1.Arsenic, which technically is a metalloid, is considered to be a toxic metal/element of concern by virtually every public health and environmental health agency across the globe including the World Health Organization, the United Nations Environment Programme, the United States Environmental Protection Agency, and the United States Centers for Disease Control and Prevention (USCDC). The Agency for Toxic Substances Disease Registry, part of the USCDC, ranks arsenic number one in its substance priority list in the US2. The rankings are based on 3 criteria including 1) the frequency of the substance’s occurrence at hazardous waste sites, 2) the toxicity of the substance, and 3) the potential for human exposure to the substance3.

Sources of Arsenic in the Environment and Potential Exposures

Arsenic is found in several different forms, both organic and inorganic, in different environmental media. This has important implications for understanding and predicting potential exposures, absorption, and toxicity, based on our current knowledge.Inorganic forms of arsenic are still widely considered the most toxic with several organic forms being considered essentially non-toxic.

Natural

Arsenic is naturally found in groundwater due to is presence in certain geological formations as well as soils and sediments. Arsenic in groundwater is usually inorganic while naturally occurring arsenic in fish and shellfish is organic, primarily arsenobetaine. Other foods such as rice and certain fruit juices contain both inorganic and organic arsenic including arsenosugars. Most foods including meats, cereals and grains, dairy products, fruits, and vegetables contain some arsenic.

Anthropogenic

There are also several sources of arsenic attributable to human activities or applications that contribute to exposure. These include mining and extractive activities, smelting, or other industrial processes. This can result in exposure to workers or contamination of the environment around such activities. Arsenic has also been used as a therapeutic agent and has shown great promise in treating acute promyelocytic leukemia4. Arsenic has long been used as a broad-spectrum pesticide and because of its anti-biotic properties has also been used to prevent pests, primarily insects from damage building materials5. For example, it has been used as wood preservative to prevent rot, decay, and insect damage. Most of these uses and applications have been phased out or banned, but copper-chromate-arsenate treated lumber is still approved for some non-residential purposes.

Another intentional application of arsenic has been the use of organoarsenicals as commercial, agricultural feed additives. This has been a direct application of concern in the poultry and swine industry with food-derived exposure concerns6. This includes several antibiotic, antiparasitic food additives such as arsanilic acid, roxarsone (3-nitro-4-hydroxyphenylarsonic acid), nitarsone (4-Nitrophenylarsonic acid), and carbarsone (p-Carbamidophenylarsonic acid). While the use of these has been discontinued in many countries, it is possible they may still be used in certain agricultural operations 7.There was considerable concern about consuming such arsenic in poultry and pork, but research suggests that these forms of arsenic are either non-toxic or much less toxic than inorganic arsenic.

Dietary Sources of Arsenic

The primary sources of exposure to arsenic in the general population worldwide are drinking water and food. Cereals and grain products are the predominant source of exposure to inorganic forms of arsenic, arsenite and arsenate, in foods8.Rice, as one of the most widely consumed grain crops, is a dominant source of food-borne exposure9. Typically, the inorganic and organic forms of mercury that accumulate in rice have their origins in the water used for irrigation. Some estimates suggest that up to 50% of total arsenic in rice is organic, usually in the form of organosugars. Concerns regarding health risks especially for potential exposure to young children consuming rice-based cereals prompted the USFDA to carry out a comprehensive risk analysis 10.The USFDA now recommends that infant rice cereals contain no more than 100 ppb (mg/kg) inorganic arsenic to reduce lifetime cancer risks 10. Various rinsing and cooking methods demonstrate effective reductions in arsenic in rice, however these same practices also tend to reduce the levels of nutrients such as iron, folate, thiamin, and niacin by as much as 70%11.

Recent pilot research we have conducted in Suriname examining a small sample of rice (n=15) and rice-cereal (n=6) products found arsenic at median concentrations of 111.4 □g/kg (IQR 89.7-139.7) and 106.5 □g/kg (IQR 84.3-111.5) in rice and rice-cereals respectively. In addition, we conducted a dietary recall survey among pregnant women (n=1,125) with specific questions regarding consumption of rice. Our survey indicates that pregnant women consume an average of 1.7 rice meals/day (median of 2 meals/day) at an average of 132 g/meal (median of 128 g/meal).This indicates that rice is much more widely and heavily consumed in Suriname than in the general population across the US, considering the average adult consumer, thus potential lifetime non-cancer and cancer risks likely far exceed those in the US. Our probabilistic risk modeling found that for non-cancer risks, which include risks for hyperpigmentation, keratosis, and vascular complications, both average and median hazard quotients exceeded 1 at 1.2 and 1.1 respectively. At least half of the population these women represent are at excess risk for these non-cancer health effects. Probabilistic modeling of cancer risk (dermal cancer) found average and median lifetime cancer risks at 5.2E-4 (5.2/10,000) and 5.1E-

4 (5.1/10,000) respectively. In fact, considering that an excess lifetime cancer risk of 1/10,000 is widely regarded as unacceptably high, approximately 90% of the population these women represent have an excess lifetime cancer risk ≥1/10,000 (1E-4).Assuming 50% of the total arsenic measured was inorganic, non-cancer and cancer risks were still excessive for some of the population with 10% at or above a hazard quotient of 1 and 80% at above a 1/10,000 lifetime cancer risk. The USEPA's Integrated Risk Information System was used for these risk analyses 12.

Several studies have examined arsenic in other staple food crops including cassava, potatoes, and sweet potatoes13-18. This includes areas with high soil concentrations of arsenic and often other heavy metals of concern. In some cases, high concentrations of arsenic have been detected but not in the root/tuber itself. Most often arsenic has been found at higher concentrations in the leaves, stem, or skin of cassava, sweet potatoes, or potatoes. This may also be because of trace amounts of residual soil on these parts of the plants. It should be noted that this has been observed in areas with very high levels of soil contamination. Some of these studies have also examined arsenic in other foods derived from these crops such as infant and toddler foods17.In one study, high levels of arsenic, especially those of concern regarding health risks, were found in rice-based cereals and while inorganic arsenic was detected, the concentrations were low in products made with pureed sweet potatoes 17. While additional research is needed to confirm these results in areas that have not been evaluated, these studies suggest that arsenic is generally not taken up in concentrations that would pose a health risk for consumers, even high consumers, of these root/tuber crops. Extra steps can be taken to avoid exposures of concern such as thoroughly washing soil from the skins, peeling the skins from the root prior to processing, cooking, and eating, and avoiding using other parts of these plant crops. However, conditions may vary from area to area, so a more thorough analysis is warranted along with robust risk modeling. Furthermore, this should include analyses examining arsenic and other elements of concern (e. g. lead, mercury, cadmium) throughout the chain of processing including food preparation and prepared food items.

Arsenic Metabolism

Finally, we will conclude with a brief overview of arsenic metabolism. Arsenic is generally thought to be metabolized and to some extent detoxified by a series of methylation reactions and redox reactionsinvolve glutathione19. Arsenate (iAsV)is typically reduced to the most toxic form of inorganic arsenic, arsenite (iAsIII). This is followed by the first methylation reaction involving s-adenosyl-L-methione(SAMe) as the methyl donor and the enzyme arsenite methyltransferase (AS3MT). This results in what are considered to be the most toxic of the monomethylated arsenic metabolites, monomethylarsonous acid (MMAIII) and monomethylarsonic acid (MMAV). A secondary methylation reaction then follows producing what are considered to be much less toxic dimethylated arsenic metabolites, dimethylarsinous acid (DMAIII) and dimethylarsinic acid (DMAV). The methylated metabolites are the primary urinary excretion products eliminating arsenic from the body. Interestingly, SAMe is largely produced from the one carbon metabolic cycle which requires folate and specifically methyltetrahydrofolate as the source of the essential methyl moiety. This suggests an essential relationship between one carbon metabolism, folate and folic acid as a food supplement, and arsenic metabolism and excretion 20, 21. There is growing evidence that folic acid supplementation along with other essential nutrients that are critical to one carbon metabolism may facilitate the methylation and elimination of arsenic and reduce its toxicity 22-25. This may well involve a gene x diet x environment interaction in the biotransformation of arsenic as polymorphisms in the AS3MT gene as well as other genes appear to be associated with arsenic sensitivity and toxicokinetics 24, 26-30.Less is known about the metabolism of many of the organic forms of arsenic especially the organosugars. Arsenobetaine which is the major form of arsenic in fish and shellfish is largely thought to be subject to little if any metabolism and is largely excreted in humans unchanged following first-order kinetics. Many of the organic forms of arsenic are believed to be comparatively non-toxic with respect to the inorganic species, but these compounds have been subject to much less toxicological research.

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