Continuing the Conversation About Arsenic

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Abstract

Chronic low-level arsenic exposure is a significant contributor to ill health and disease. However, at this time, quantification of the effects of this exposure appears virtually impossible. In a continuation of my editorial on arsenic published earlier this year, this editorial looks at arsenic's mechanisms of damage, more disease correlations, sources of exposure, and early signs for detection of arsenic toxicity.

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Introduction

Earlier this year (*IMCJ 23.1)* I wrote an editorial, "Time to Recognize and Address the Serious Arsenic Problem." In that editorial I reviewed research suggesting that arsenic is an underappreciated contributor to a substantial amount of disease. I included graphics showing dose-dependent relationships of arsenic with the prevalence of cancer, diabetes, and heart disease. The number of people affected is quite concerning, since they shows that a substantial portion of the population exceeds the thresholds for increased risk for these diseases.

I have continued to look at the research on arsenic to try to better understand how arsenic causes disease, other disease associations, where arsenic comes from, and early indications of toxicity. Studying arsenic is hugely challenging due to surprising inconsistency in epidemiological research, inconsistency in identifying or even specifying arsenic speciation, and inexplicably huge variations in the amount of arsenic contamination measured in water, rice, and chicken. Nonetheless, I am continuing to try to make sense of the research. Arsenic is clearly a major contributor to ill health and disease. However, quantification of the degree of increased risk appears virtually impossible.

Mechanisms of Damage

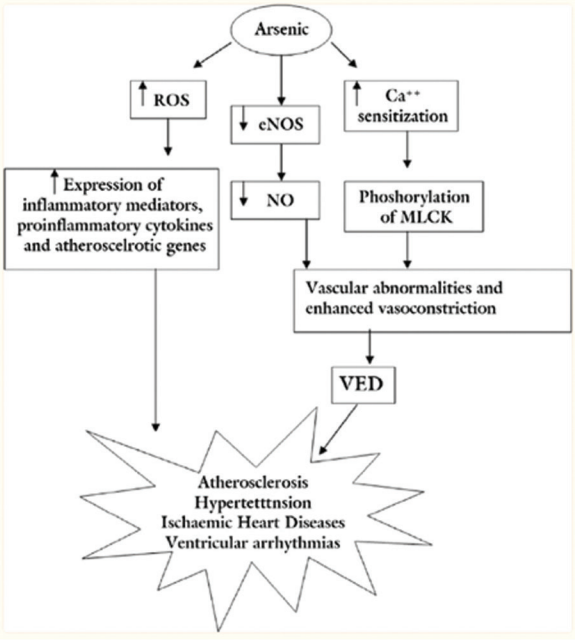
The list of documented and possible mechanisms of arsenic damage is surprisingly long. Table 1 lists what appear to me to be the key underlying effects of arsenic that cause a huge range of physiological dysfunctions.

Singh et al[1] published an excellent review article in which they included several diagrams illustrating the many pathways by which arsenic damages physiology and induces disease. One of them, in the context of cardiovascular dysfunction, is reproduced here as Figure 1.

Table 1. Arsenic-Induced Dysfunctions that Underlie Its Role in Chronic Disease

- Binding to sulfhydryl groups, disrupting many enzymes
- Substituting for phosphorus in many biological reactions, thus impairing their function
- Impairing mitochondrial function
- Increasing oxidative stress, which increases damage indiscriminately

Figure 1. Pathological Mechanisms Involved in Arsenic-Induced Cardiovascular Dysfunction[1]



Abbreviations: eNOS, endothelial nitric oxide synthase; MLCK, myosin light-chain kinase; NO, nitric oxide; ROS, reactive oxygen species; VED, vascular endothelial dysfunction.

Figure 2. The Diverse Damage From Arsenic[3]

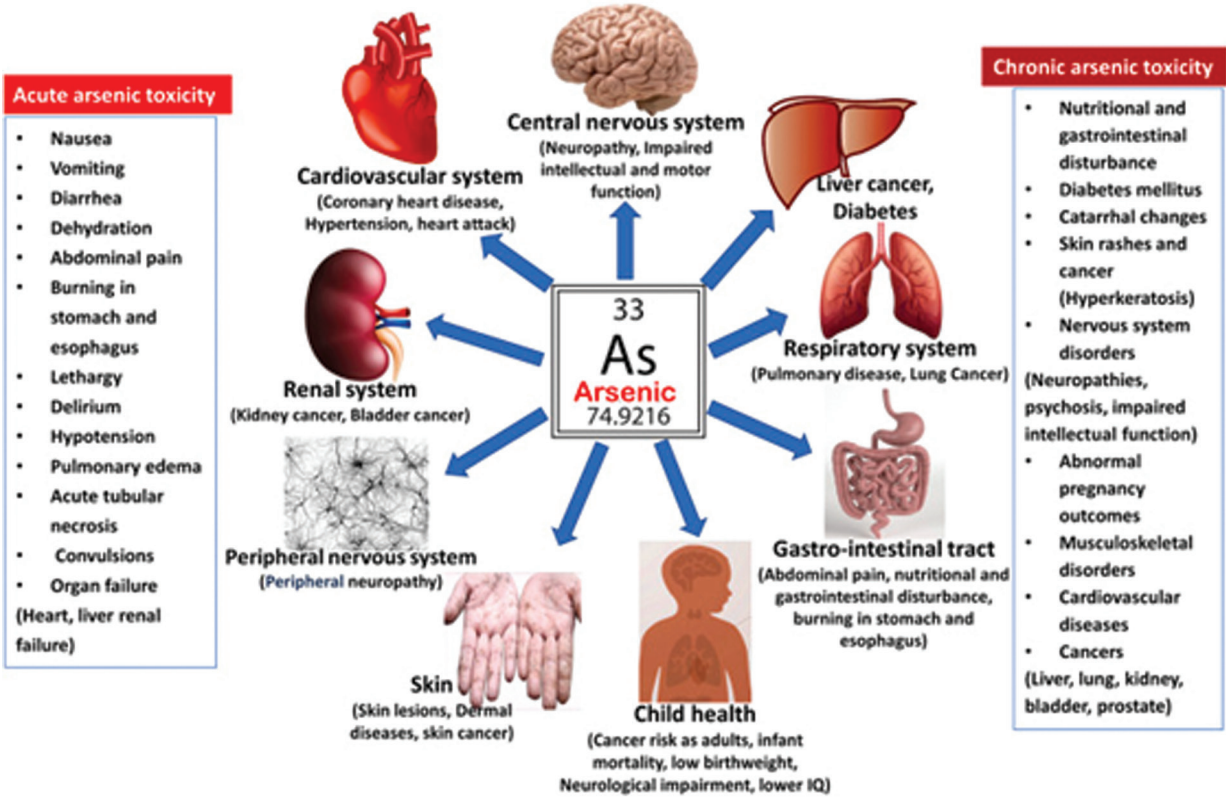
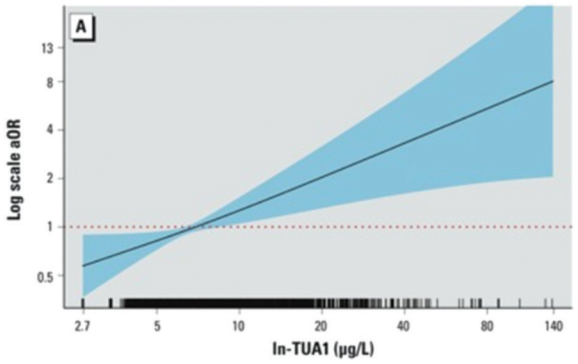
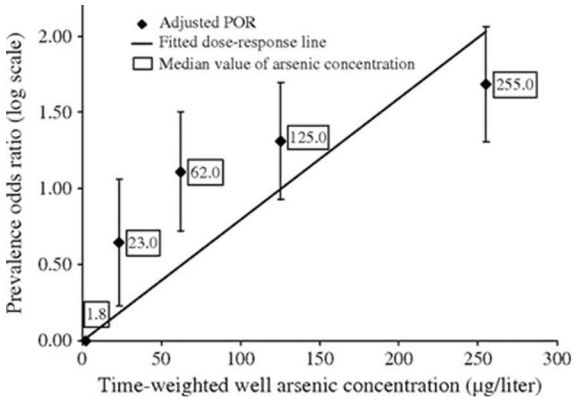


Figure 3. Arsenic and Varicella-Zoster Virus IgG[4]



Abbreviations: aOR, adjusted odds ratio; TUA1, total urinary arsenic, as the sum of arsenite, arsenate, monomethylarsonic acid, and dimethylarsinic acid.

Figure 4. Well-Water Arsenic and Premalignant Skin Lesions[5]



Abbreviation: POR, prevalence odds ratio.

I was especially intrigued by research showing the mitochondrial damage induced by arsenic. Of particular interest is that arsenic inhibits succinate dehydrogenase, a key enzyme in both the citric acid cycle and oxidative phosphorylation.[2] However, this research was only performed in vitro and needs in vivo assessment.

Arsenic and Disease Risk

The more I looked at disease associations with arsenic, the more I found. The challenge is the huge inconsistencies between studies. Figure 2 shows an excellent graphic from Rahaman et al[3] showing the diversity of arsenic's damage.

I have found several more studies showing a dose-dependent relationship between arsenic and disease risk; data from one such study is shown in Figure 3 for shingles, caused by reactivation of the varicella-zoster virus. Note that these data are for *total* arsenic, not just the most toxic forms.

A study (data in Figure 4) looked at well-water arsenic and premalignant skin lesions in Bangladesh. The authors corrected for gender, age, education, cigarette smoking, sun exposure in males, and land ownership.

Before you dismiss this study because it is from Bangladesh with known high levels of arsenic, be aware

there are many areas in the US with elevated arsenic in drinking water, discussed below.

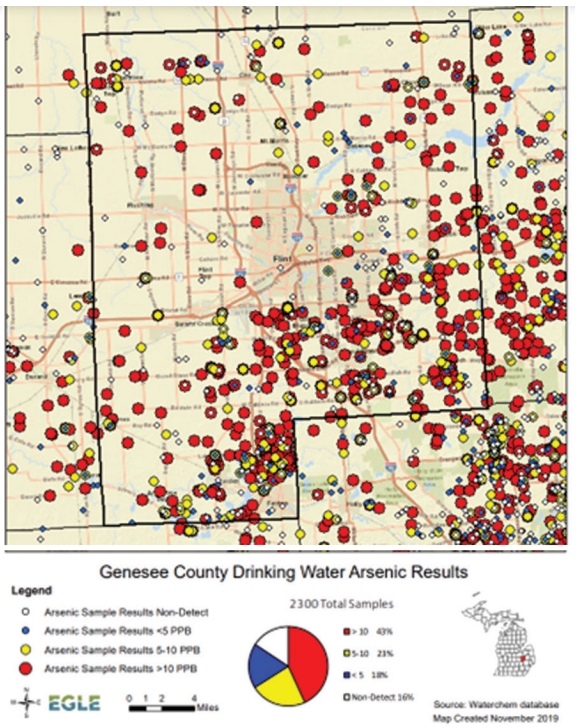
Sources of Arsenic

The average daily consumption of total arsenic per person in the US is approximately 40 µg.[6]

Water

A simple search of the internet will find many US state and U.S. Geological Survey studies and maps showing that elevated arsenic is common in drinking water in the US, especially well water. An illustrative example comes from the state of Michigan. Figure 5 shows the level of arsenic in drinking water in Genesee County where the city of Flint is located. While the lead contamination there received a lot of media attention, I assert that arsenic is an even worse problem—43% of the drinking water there exceeded the World Health Organization standard of 10 µg/L! And, as I asserted in my earlier editorial, this threshold is too high, due to genetic susceptibilities and common nutritional deficiencies that increase the risk of arsenic-induced health issues. Not included in Figure 5 is that several of the wells were above 50 µg/L arsenic.

Figure 5. Arsenic in Genesee County Drinking Water[7]

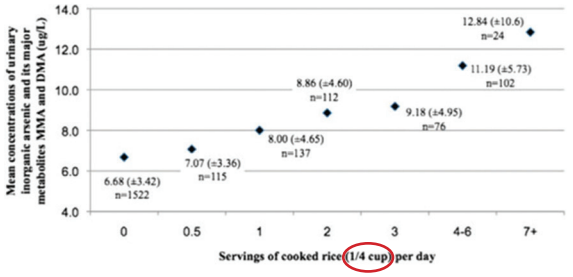


Food

Rice, chicken, and fish are considered the primary food sources of arsenic.

Rice. As can be seen in Figure 6, there is a dose-dependent relationship between rice consumption and urinary arsenic concentration. On first glance the numbers do not look too bad—until you notice that the servings per day can be misleading—they are the number of *¼ cups* per day, not number of cups per day. Note that these data are from the US and that arsenic in rice is almost all the highly toxic inorganic forms.

Figure 6. Urinary Arsenic Concentration Correlates With Rice Consumption[8]



Chicken. The U.S. Food and Drug Administration has established permissible levels of arsenic: 0.5 ppm (500 µg/kg) in eggs and uncooked edible tissues of chickens and turkeys and 2 ppm (2000 µg/kg) in certain uncooked edible byproducts of swine.[9] These surprisingly high permissible numbers provide justification for the first several pages of an internet search for arsenic in chicken being dominated by links saying chicken is safe from arsenic—all from various chicken-grower associations.

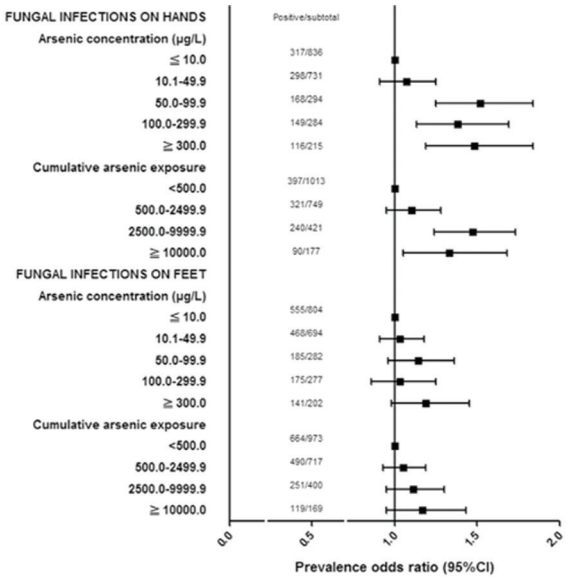
Determining *current* arsenic concentration in US chicken has proven surprisingly difficult. In the past, arsenical compounds were part of the standard of care for raising chickens. Many studies on arsenic in chicken are available from before 2015—about the time the U.S. Department of Agriculture removed the recommendation of using arsenic in chicken husbandry. I could not find a relevant US study after 2016. I did however find recent studies of arsenic in chicken from other countries. For example, sauced chicken from China contains 0.5 to 1.5 µg/kg.[10] In contrast, chicken breasts from India contained 214 to 2228 µg/kg—a three-fold order of magnitude difference![11]

Fish and Shellfish. The other primary source of arsenic is from fish and shellfish, in which it is bound to betaine. Since arsenobetaine has very low toxicity, a marine contribution to arsenic toxicity is considered insignificant. However, recent animal research has shown significant conversion in vivo of arsenobetaine to inorganic arsenic.[12] Human research suggests limited breakdown of arsenobetaine to the toxic inorganic and monomethylarsonic acid forms.[13] Interestingly, this study showed that some forms of shellfish have potentially significant concentrations of inorganic arsenic and monomethylarsonic acid, with blue mussels being the worst.

Other

There are many other sources of arsenic exposure, highly dependent upon location and activities.[14] These

Figure 7. Arsenic and Fungal Infections[15]



include living or working near mining or smelting; being near coal burning; working with wood preservatives, insecticides, rodenticides, and herbicides; and some prescription drugs.

Earliest Signs of Arsenic Toxicity

One of the biggest challenges of recognizing chronic low-level arsenic toxicity is the lack of symptoms. While urine arsenic concentration is the current standard for detecting arsenic toxicity, the threshold numbers are diverse across countries and agencies and do not appear consistent with current research. As can be seen from the graphics in this and my earlier editorial, the threshold for increasing risk for various diseases ranges widely. Compounding this challenge is the short half-life of arsenic. In general, arsenic in the urine primarily indicates exposure during the previous 1 to 4 days.

The short half-life of arsenic led me to search for other ways to detect potential toxicity as soon as possible after exposure (Thanks to Dr. Lyn Patrick for bringing hyperkeratosis to my attention.). The earliest signs of arsenic exposure tend to be dermal lesions, such as hyperkeratosis; premalignant lesions (Figure 4); and fungal infections (Figure 7). To illustrate this point, Figure 7 shows a graphic from a study in Taiwan on fungal infections. Note that fungal infection on the hands starts to increase at 10 μg/L *total* arsenic and starts at a higher arsenic concentration on the soles.

Several US studies have looked at the daily intake of *total* arsenic at which hyperkeratosis can be detected. The numbers ranged from 3 to 6 μg/kg/d.[16] The U.S. Environmental Protection Agency reference dose for *inorganic* arsenic is 0.3 μg/kg/d based on effects on the skin (hyperpigmentation and keratosis).[17] I have tried to determine the percentage of total arsenic is the most toxic inorganic and monomethylarsonic acid forms and have not found anything definitive. My best estimate is 10% to 20%. This estimate is consistent with the U.S. Environmental Protection Agency reference dose numbers and the total arsenic threshold for skin manifestations.

Checking palms of the hands and soles of the feet for roughness, hyperkeratosis, and premalignant lesions can be a useful early guide for suspected arsenic exposure.

Conclusion

Having now looked at a lot of research, I think it likely that the lack of attention to water contaminants and dietary arsenic exposure in study populations is an unrecognized confounder in a lot of disease research, especially epidemiological research.

I believe we must consider low-level arsenic toxicity in every patient. Early signs, like palm and sole skin lesions, need to be checked. First morning urine—while eating their normal diet and drinking their normal water—should be measured for arsenic. If the urinary arsenic is greater than 10 ug/L, it should be speciated. You are likely wondering about arsenic from fish and shellfish. The current standard is to not eat fish or shellfish for at least 2 days before measuring urinary arsenic. However, if humans are converting some of the arsenobetaine to inorganic arsenic and monomethylarsonic acid and the fish/shellfish do contain small amounts of the toxic forms of arsenic, perhaps we should rethink this recommendation to avoid fish and assuming that the high levels are only relatively safe arsenobetaine.

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