ANNUAL REVIEWS

Annual Review of Pharmacology and Toxicology

Arsenic: A Global Environmental Challenge

Qiao Yi Chen[1] and Max Costa[2]

[1]Department of Cell Biology and Genetics, School of Basic Medical Sciences, Xi'an Jiaotong University, Xi'an, Shaanxi 710049, China

[2]Department of Environmental Medicine, New York University School of Medicine, New York, New York 10010, USA; email: Max.Costa@nyumc.org

Annu. Rev. Pharmacol. Toxicol. 2021. 61:47–63

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

https://doi.org/10.1146/annurev-pharmtox-030220-013418

Keywords

arsenic, contamination, environment, resistance, mitigation

Abstract

Arsenic is a naturally occurring metalloid and one of the few metals that can be metabolized inside the human body. The pervasive presence of arsenic in nature and anthropogenic sources from agricultural and medical use have perpetuated human exposure to this toxic and carcinogenic element. Highly exposed individuals are susceptible to various illnesses, including skin disorders; cognitive impairment; and cancers of the lung, liver, and kidneys. In fact, across the globe, approximately 200 million people are exposed to potentially toxic levels of arsenic, which has prompted substantial research and mitigation efforts to combat this extensive public health issue. This review provides an up-to-date look at arsenic-related challenges facing the global community, including current sources of arsenic, global disease burden, arsenic resistance, and shortcomings of ongoing mitigation measures, and discusses potential next steps.

INTRODUCTION

Notoriously known as the king of poisons and the poison of kings, arsenic (As) served as a discreet and high-profile poison for the ruling class during the Middle Ages and Renaissance (1, 2). While the earliest scientific studies on arsenic predominantly focused on its use as a cure for fever, agues, and periodic headaches, its reputation as a potent poison undeniably paved the way for later toxicological studies. Since the first published paper in 1786, 32,346 reports and studies have materialized, most of which are from the last few decades and are centered around the toxicity and carcinogenicity of this International Agency for Research on Cancer class I carcinogen (3).

Arsenic is a ubiquitous metalloid found naturally in and composing approximately 0.00015% of the earth's crust. Commercial sources of arsenic are often extracted from iron (Fe)-, nickel-, and cobalt-containing minerals. Arsenic is commonly used in electronic devices, in pesticides, and as the treatment of promyelocytic leukemia. Thus, in addition to natural corrosion and weathering of rocks and mineral ores, anthropogenic sources from human activity have reinforced the presence of arsenic in the environment. Globally, about 200 million people are exposed to potentially toxic levels of arsenic, and substantial efforts have been expended on research studies and potential alleviation methods. This review presents a global perspective on current challenges and opportunities with respect to arsenic-related public health issues and mitigation strategies.

GLOBAL DISTRIBUTION OF ARSENIC AND DISEASE BURDEN

Exposure to inorganic and organic arsenic compounds continues to pose substantial public health concerns for hundreds of millions of people around the globe (4). The provisional guideline for arsenic in drinking water, as set by the World Health Organization (WHO) back in 1993, is 10 μg/L, which is in accordance with the suggested total 15 μg of inorganic arsenic intake per kilogram body weight. In 2001, based on dose-response risks of arsenic-induced bladder and lung cancer found in Taiwan, the United States Environmental Protection Agency revised the maximum contaminant level of drinking water from 50 μg/L, as set by the National Research Council back in 1999, to 10 μg/L (5). Extensive research in more than 70 countries has revealed that the groundwater concentration of arsenic varies greatly by region, from 0.5 to 5,000 ppb (6, 7) (see **Figure 1**). The most serious arsenic contamination has been found in Brazil, Cambodia, Afghanistan, Australia, and Bangladesh (8).

Current research has demonstrated that arsenic is capable of eliciting damage to every organ in the human body through the process of arsenic metabolism (**Figure 2**). Chronic arsenic exposure has been shown to elicit a wide range of clinical complications, including skin disorders, diabetes mellitus, cardiovascular disease, peripheral neuropathy, cognitive impairment, hepatic and renal dysfunctions, and reproductive complications. Notably, arsenic accumulation is most prominent in the liver, kidneys, and muscles (**Table 1**). In addition, high concentrations of arsenic have been shown to promote cancers of the bladder, lung, skin, kidney, and prostate (9). However, detailed dose-response and large-scale longitudinal studies are warranted to understand the effects of low and moderate arsenic exposure. In India, low (<50 μg/L) levels of arsenic have been detected in millions of aquifers, yet certain exposed populations do not show arsenic-induced skin lesions (10). However, skin lesions such as black foot disease, melanosis, and keratosis typically develop 5–10 years after chronic arsenic exposure; thus, follow-up studies may be necessary. In addition, there is evidence that exposure to 10 μg/L of arsenic can lead to a 0.1–0.3% cancer incidence (11). One study reported that since 2000, exposure to 10 μg/L arsenic has led to an increase of 4.51 and 2.91 lung and bladder cancer cases per 1,000,000 people, respectively (12, 13).

Particular groups of people are especially vulnerable to arsenic-related health risks, including pregnant women, developing children, and those with underlying genetic risk factors. One study

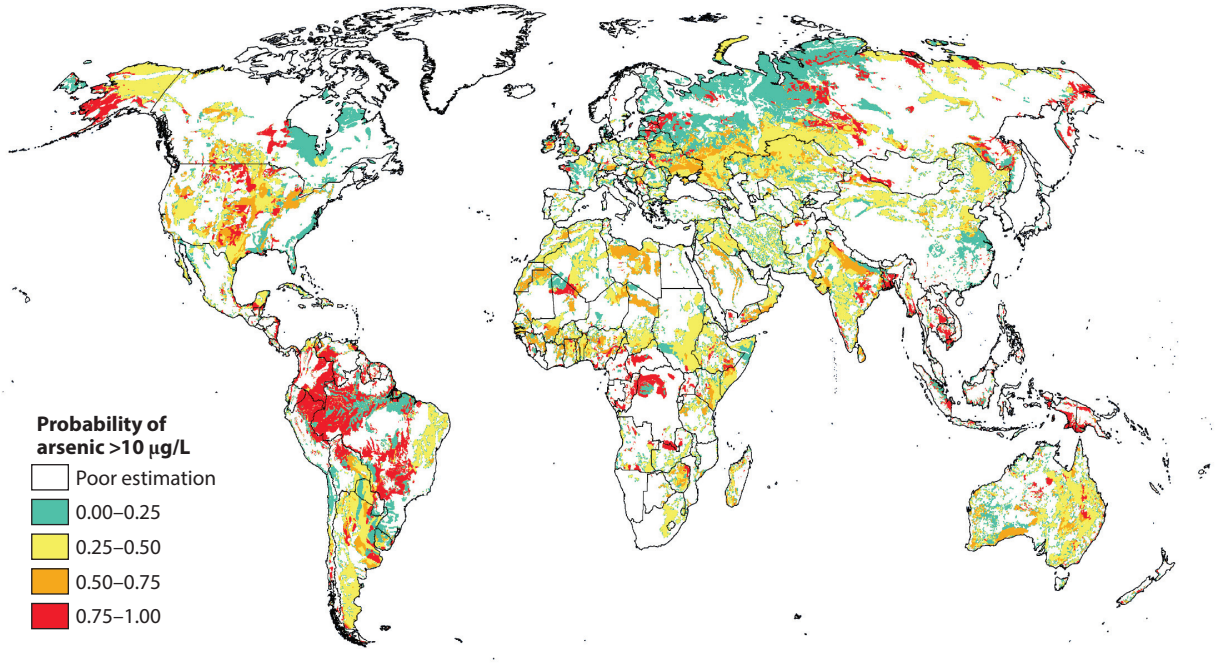

Figure 1

Map of global arsenic contamination. The map illustrates the extent of arsenic contamination around the world. Modified from Reference 132, copyright 2021 Eawag (**https://www.eawag.ch/en/research/humanwelfare/drinkingwater/wrq/risk-maps**).

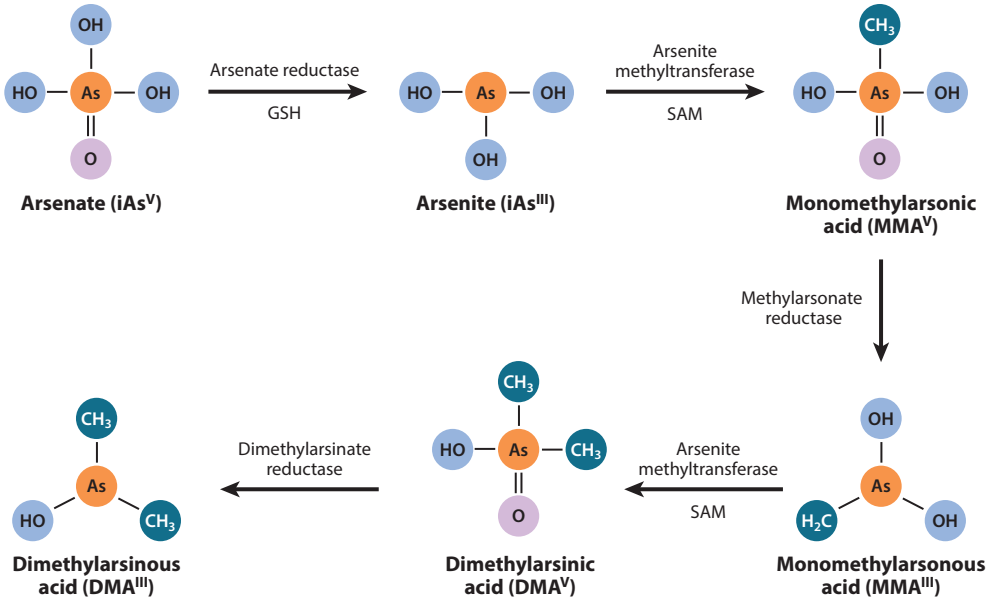

Figure 2

Metabolism of arsenic in human cells. The illustration depicts the pathway of arsenic metabolism in the human body. Abbreviations: GSH, glutathione; SAM, *S*-adenosyl-L-methionine.

Table 1 Arsenic species found in different human organs and blood

Organ	Concentration, μg/g dry weight (percentage of total arsenic)				
	As(III)	DMA	MMA	As(V)	Mb + As(V)
Liver	122.00 (83%)	5.91 (4%)	14.7 (10%)	2.94 (2%)	23.55 (16%)
Kidneys	19.95 (75%)	1.60 (6%)	4.52 (17%)	0.53 (2%)	6.65 (25%)
Muscle	9.17 (75%)	0.73 (6%)	1.96 (16%)	<LOQ	2.69 (22%)
Heart	9.05 (77%)	0.64 (5%)	1.61 (14%)	<LOQ	2.25 (19%)
Spleen	9.50 (81%)	0.59 (5%)	1.65 (13%)	<LOQ	2.24 (18%)
Pancreas	9.18 (82%)	0.45 (4%)	1.34 (10%)	<LOQ	1.79 (14%)
Lung	9.46 (85%)	0.45 (4%)	1.11 (10%)	<LOQ	1.56 (14%)
Cerebellum	5.15 (47%)	1.60 (19%)	3.76 (30%)	<LOQ	5.36 (49%)
Brain	4.41 (53%)	1.10 (18%)	2.65 (27%)	<LOQ	3.75 (45%)
Skin	1.62 (56%)	0.34 (15%)	0.91 (28%)	<LOQ	1.25 (43%)
Hemolyzed blood	0.224 (53%)	0.0539 (13%)	0.135 (32%)	0.009 (2%)	0.198 (47%)

The table compares the amount of arsenic accumulation in different human organs and blood. Data from Reference 131. Abbreviations: As, arsenic; DMA, dimethylarsinic acid; LOQ, limit of quantification; Mb, DMA + MMA; MMA, monomethylarsonic acid.

reported that children under the age of three experience greater chances of (factor of three) arsenic exposure in comparison with adults. One reason may be the consumption of infant rice cereal, which has been shown to contain arsenic. According to data collected by the National Health and Nutrition Examination Survey, the amount of urinary arsenic detected parallels the average amount of rice consumed. Children in the United States between the ages of 6 and 17, of Asian, Mexican, and African descent, were found to have greater urinary arsenic than white children (14). Of note, arsenic exposure in utero or during early childhood development has also been shown to lead to increased rates of bladder and lung cancer later in life (15, 16). Even in the United States, rice has high arsenic levels because it is grown in farm fields that used to grow cotton and in which arsenic was once used as a pesticide. Moreover, occupation, sex, lifestyle, and dietary preferences as well as cultural factors can also play a role in the degree of arsenic exposure.

Unfortunately, the plight of arsenic contamination is not limited to physical health. An extensive public health crisis can cause crippling effects to the economy. A multitude of arsenic-related health outcomes have been shown to lead to premature death, especially in poverty-stricken areas (17). In Bangladesh alone, approximately 9,136 deaths occurred and 174,174 disability-adjusted life years were lost per year (18). The estimated economic loss as a result of arsenic-related mortality (1 in 16 adult deaths) is equivalent to $13 billion over a 20-year period (19). Without adequate and effective mitigation measures, arsenic-related diseases and economic burden would most likely worsen in a perpetuating cycle.

SOURCES OF ARSENIC

Arsenic is a naturally occurring element perpetually found in air, soil, water, plants, animals, and rocks and is predominantly released into the environment through weathering, rock erosion, volcanic eruption, and forest fires. Notably, arsenic is a major component in more than 200 different types of minerals (20). In fact, 99% of arsenic has been found as a constituent in rocks and minerals (21). Specifically, arsenic is mainly present in sulfidic minerals such as arsenopyrite, which predominantly exists in anaerobic conditions, as well as in other rock-forming minerals, including silicate, phosphate, sulfide, and oxide (22). Other important arsenic-containing minerals include cobaltite (CoAsS), arsenolite (As_2O_3), olivenite (Cu_2OHAsO_4), orpiment (As_2S_3),

and other minerals (22, 23). The dissolution of arsenic-containing minerals can leach into and contaminate groundwater (24, 25). Arsenic can also be found in sediments with high levels of Fe oxide and/or other reducing agents, most likely in the range of 3–10 mg/kg (7).

Groundwater makes up 97% of total global fresh water and is the main source of human drinking water. The degree of arsenic contamination of surface water and groundwater is generally a result of the amount of arsenic present in the soil, which exists as either As(V) or As(III) under oxidizing or reducing conditions, respectively. Of note, the average concentration of arsenic found in soil is approximately 3–4 mg/kg (26). Under oxidizing conditions, inorganic arsenic can be methylated into monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), and trimethylarsine oxide by microorganisms (27, 28). Under reducing conditions, arsenic can be released from river sediments and into groundwater (29). Of note, the release of arsenic from Fe oxides in aquifer sediments is one of the predominant reasons for groundwater contamination. A considerable amount of research has been centered around arsenic-related outcomes based on drinking water exposure. However, there is still much to be addressed regarding the sources and toxicokinetics of other arsenic species.

Little is known about the potential effects and toxicokinetics of a vast array of arsenic species such as arsenoproteins, arsenolipids, thiolated arsenic compounds, and arsenobetaine. Notably, complex organic arsenic compounds, including dimethyl(ribosyl)arsine oxides, tetramethylarsonium salts, and arsenocholine, have been found in marine ecosystems. Interestingly, most of the arsenic found in seawater, at concentrations of 1–8 μg/L, is not in solution due to arsenic's ability to be adsorbed onto particulate materials or taken up by marine organisms, including algae, fish, mollusks, and phytoplankton (30). Arsenic taken up by phytoplankton is quickly metabolized into organic compounds, which are the dominant form (99%) of arsenic found in fish and other marine invertebrates such as flounder, lobsters, clams, and sharks. Specifically, fish and algae are known to contain arsenobetaine as well as arsenosugars, arsenoproteins, and arsenolipids (31–33). Fish can contain up to 100 times more total arsenic than other types of foods such as rice (32–34). Coupled with the variety of arsenic species present, detailed studies are necessary to examine the potential health effects of these poorly understood arsenic forms. Currently, little is known about arsenobetaine except that it is considered to have low toxicity and, through microbial metabolism in costal seawater sediments, it can transform into more toxic forms of inorganic arsenic and methylarsonic acid (30, 35, 36). Additionally, seaweed, an emerging organic soil fertilizer alternative and feed additive for dairy farming, has been shown to contain significantly higher concentrations (up to 100 mg/kg) of arsenic than grains (37, 38). While most of the arsenic species are arsenosugars and considered to be of low toxicity, these compounds can eventually degrade into toxic inorganic arsenic in soil (39).

Anthropogenic sources of arsenic include mining, the use of arsenical pesticides and fungicides, burning of fossil fuels, and pharmaceutical drugs (40). The first documented use of arsenic in medicine was between 469 and 388 BCE when Hippocrates used sulfides of arsenic to treat ulcers. Arsenic has also been used in traditional Chinese medicine for more than 2,000 years. Elaborate documentation of its various forms, functions, and applications can be found in the classic herbal medicine book *Shennong Bencaojing*, written between about 200 and 250 CE. In the eighteenth century, the Fowler solution, composed of As_2O_3 dissolved in potassium bicarbonate, was used for treating intermittent fevers and later for various infectious diseases and chronic myelogenous leukemia (41–45). In the 1970s, researchers from Harbin University discovered the remedial effects of As_2O_3 for acute promyelocytic leukemia (APL), which quickly emerged as a promising cancer therapeutic agent in Western medicine (46, 47). Since then, the therapeutic effects of arsenic for cancer have been intensively studied. Current research suggests that in addition to APL,

As_2O_3 may be a promising treatment for solid tumors, including lung, breast, gastric, cervical, bladder, pancreatic, nasopharyngeal, and ovarian cancer (48–55).

In addition, arsenic-based drugs such as nitarsone and roxarsone have long been fed to chickens in the United States to promote growth, pigmentation, and disease prevention (56, 57). A report from 2013 indicated that for US consumers, arsenic intake from poultry alone contributed to 0.00144 μg/kg of arsenic intake, large enough to result in 124 extra lung and bladder cancer cases (58). Similar studies have prompted concern for consumers, and in 2013 and 2015, roxarsone and nitarsone were eliminated as feed additives by the US Food and Drug Administration (FDA). Other food sources prompting concerns about arsenic contamination include grains, rice, and vegetables. Contaminated groundwater used to irrigate crops and soil has been shown to lead to significant accumulation of arsenic in cultivated foods (59). Notably, rice (*Oryza sativa L.*) is one of the most efficient accumulators of arsenic, amassing concentrations approximately 10 times more than wheat. Due to its similarity with silicic acid, arsenic is able to be transported into the grains through silicon transporters under flooded conditions. Rice also serves as a staple food product for half of the world's population, particularly for those that reside in Southeast Asia, Latin America, and sub-Saharan Africa. While direct consumption of rice grains in the United States is significantly less compared to other countries, rice-derived products are widely used in processed foods (60, 61). In fact, any food with rice as a component, including cereal bars, rice milk, rice crackers, baby cereal, syrup, and rice bran, is currently defined as a rice product by the FDA (62). And in consideration of the extensive research on the adverse health effects of arsenic, several regulatory agencies have proposed setting a limit for inorganic arsenic content in food products. The FDA has proposed a 100-ppb limit for infant rice cereal, while the European Commission has recommended an inorganic arsenic limitation for a variety of foods such as rice cereal, milled rice, parboiled and husked rice, rice crackers and cakes, and so on. (63). Setting regulatory limits for arsenic in food products is an important step toward reducing human exposure and may be especially important for populations that depend on rice as a staple product.

ARSENIC TOXICITY AND THE MICROBIOME

The human body harbors a vast array of microorganisms, including bacteria, fungi, archaea, viruses, and other microbes—together, these are known as the microbiota. The microbiome includes all the genes that a person's microbiota contains, and can be used interchangeably with the term microbiota. Research has revealed that the microbiome can interact with host cells and functions to provide nutrients, prevent diseases, and regulate the immune system (64). The microbiome has long been known to interact with arsenic. The impact of their interactions can be categorized into three main types: no effect, disruption of microbiome, and modification of arsenic's toxicological properties (65). In the first type of interaction, neither the microbiome's integrity nor the toxicological property of the toxicant is affected through their interaction. In the second type, arsenic exposure is capable of killing members of the microbiome and perturbing its functions. Changes in the microbiome can directly influence the host's toxic response pathways. In the third type, the microbiome is capable of metabolizing arsenicals and limiting toxicity to the host tissues, as well as generating energy (66–68).

The degree of arsenic toxicity and motility depends on its oxidation state. Specifically, pentavalent arsenate, As(V), is both less toxic and less mobile than trivalent arsenite, As(III) (69, 70). As(III) is more toxic than As(V) because As(III) can bind strongly to vicinal sulfhydryl groups in proteins. In addition, trivalent methylarsenicals are more toxic than trivalent arsenite, pentavalent methylarsenicals, and inorganic arsenate (71, 72). In other words, arsenic speciation and methylation can directly influence the toxicity, bioavailability, and bioaccumulation of arsenic in the environment.

This suggests that the integrity of the microbiome, both in the environment and in the host body, is critical for defining arsenic toxicity and mobility.

To illustrate the importance of a healthy microbiome in resisting arsenic toxicity, a study conducted by Coryell et al. (73) purposely depleted the microbial biomass of mice through antibiotic treatment prior to subjecting them to arsenic exposure. The researchers found that a disrupted microbiome led to reduced arsenic excretion and increased accumulation in the host liver and lung tissues. Interestingly, in the natural environment, arsenic and antibiotics are frequently found together. For example, the use of arsenic in conjunction with antibiotics in livestock means that both can be easily found in agricultural fields. To study the combined effects of arsenic and antibiotics, one study treated *Metaphire sieboldi* earthworms with both arsenic and sulfamethoxazole, an antimalarial agent, and found significant changes in the microbial community of the earthworm gut, as reflected by an increased abundance of *Bacteroidetes* and *Proteobacteria* (74). Notably, treatment with both arsenic and sulfamethoxazole led to increased diversity and a greater amount of antibiotic-resistant genes (ARGs) in the earthworm. The accumulation of ARGs in the environmental microbiome can lead to the emergence of multidrug-resistant pathogens, posing a tremendous risk for human health.

However, in the process of oxidizing arsenicals, the microbiome can be easily disrupted. Arsenic-induced dysbiosis, or a microbial imbalance, has been associated with various diseases, including obesity, diabetes, Parkinson's, and cancer (75, 76). Specifically, intestinal colonization with *Lachnospiraceae* has been discovered in the development of diabetes in obese mice and has been found to be enriched through arsenic exposure (77, 78). In addition, *Bacteroides* and *Bifidobacterium* are known to play crucial roles in immune system regulation, and levels of both have been documented to be reduced by arsenic exposure (79–81). In a study using 8-week-old male mice, Tikka et al. (76) demonstrated that arsenic exposure (at 3 and 6 months) is capable of altering the gut microbiome as well as damaging the villi structure and epithelial layer of the intestinal jejunum region. Interestingly, the study also found that dendritic cells, inflammatory cytokines, macrophages, and B-catenin, a prominent colon cancer marker, all increased as a result of arsenic exposure. These results suggest that arsenic-induced changes in gut microbial composition may be an important factor in immune system regulation. Similarly, low arsenic exposure has also been shown to promote dysbiosis in zebra fish through the disruption of microbial structure and diversity (82).

Early life is an important stage for gut microbiome development in humans, and interference with its maturation can lead to a risk of developing lifelong diseases such as asthma, obesity, and allergy (77, 78, 83, 84). In a study based in New Hampshire, urine and stool samples from 204 infants were analyzed for a potential correlation between urinary arsenic concentration and stool microbiome composition (77). Results suggested that formula-fed (higher arsenic exposure from both formula and water) male infants showed higher susceptibility to arsenic-induced changes in their microbiota (77). Interestingly, arsenic-induced, sex-specific changes in the human body are not limited to the microbiome but also extend to the transcriptome level (85). In Bangladesh, high concentrations of arsenic in drinking water have been shown to be associated with a higher abundance of *Enterobacteriaceae* in the microbiome of 4–6-year-old children (86). Conversely, *Enterobacteriaceae* abundance is negatively associated with increased arsenic exposure in US infants (77). Some suggest that nutrition may be a determining factor for between-subject variability. As a case in point, mice with zinc deficiency undergo exacerbated arsenic-induced changes in microbiome composition, while Fe supplementation protects host microbiome integrity (87–89). In addition, one particular study introduced human fecal matter to germ-free mice and found that different microbiome composition led to significant variability in mice survival after arsenic exposure (73, 90). In other words, changes in the gut microbiome in response to arsenic exposure are

multifaceted in that dose, length of exposure, host sex, and dietary micronutrients may all play a role in the overall outcome.

ARSENIC RESISTANCE

Over the past thousands of years, like all species on the planet, humans have endured strong natural selection. In parts of Europe, some populations have developed lactose-tolerant genes, and some in parts of Africa have evolved to become resistant to malaria. Recently, Schlebusch et al. (91) reported evidence of human adaptation to arsenic. It is interesting to note that almost every organism has some type of mechanism for arsenic detoxification that involves transport and elimination. In the human body, inorganic arsenic is first methylated into MMA and then DMA, which can then be readily expelled from the body through urine. MMA is the more toxic form, and concentrations of this form can vary by population. Notably, Schlebusch et al. found that indigenous populations living in the Andes had significantly lower MMA in their urine. Arsenic methyltransferase (*AS3MT*) is responsible for arsenic methylation, although the efficiency of each of its alleles may differ from population to population, which is the basis for the human-arsenic adaptation hypothesis (92–94). Specifically, the study reported that indigenous residents in the Andes who have been exposed to high levels of arsenic in drinking water for thousands of years demonstrated higher methylation efficiency compared to other populations such as Native Americans, Asians, Peruvians, and Colombians. They also showed a selection signal for higher frequencies of *AS3MT* haplotypes, which suggests that the *AS3MT* locus may have been a selection target for arsenic adaptation (91).

ARSENIC MITIGATION STRATEGIES

Various types of mitigation programs have been introduced to provide safe water for communities affected by arsenic contamination. Simple and straightforward methods suitable for community settings have included the use of well switching, hand pumps, sand filters, rainwater harvesting, and solar disinfection. In Bangladesh, well testing has been an effective mitigation measure that marked wells with high arsenic concentrations, raised awareness, and encouraged affected residents to switch to nearby shallow wells with low arsenic content. However, shallow wells without appropriate treatment are more likely to be contaminated and promote diseases such as diarrhea, typhoid, cholera, and hepatitis (8). In addition, well switching proved to be a burdensome method due to long travelling distances, hot weather, and malnutrition among women who were in charge of fetching water (94, 95). Other water sources included deep ground, dug wells, surface water, and rainwater. Groundwater from deep-tube wells (>150 m) generally has less arsenic content (1% detected with >50 ppb) but is costly to exploit and often has high concentrations of dissolved Fe and manganese (Mn) (8). Open dug wells have low arsenic contents due to their inherent oxidative environment (96). Unfortunately, dug-well water has proven to be unpopular due to its objectionable smell and vulnerability to bacteriological contamination, similar to limitations of surface water from ponds, rivers, and lakes. The implementation of rainwater harvesting requires installation of specialized roofs and large storage tanks that are costly, and it has proved to be unpredictable due to fluctuating rainwater distribution from year to year. In addition, the dissolution of metals such as zinc and lead in acidic rainwater requires special attention. More recently, a numerical groundwater modeling software (GMS10.2) was developed to predict water flow and arsenic transport (97). Specifically, this technology allows for the assessment of potential arsenic content in deep and shallow aquifers. Current data indicate that since arsenic

moves in a downward manner, deeper aquifers are considered unsafe for drinking and irrigation. Beyond these findings, water monitoring using advanced numerical modeling may prove to be a cost-effective decision-making tool for future mitigation strategies.

In addition to alternative water sources, sophisticated arsenic elimination techniques have been developed, including adsorption, coagulation/membrane filtration and purification, oxidation and reduction, microorganism oxidation, ion exchange, reverse osmosis, and coprecipitation. Compared with As(V), As(III) is more toxic and difficult to remove from water; therefore, oxidation followed by adsorption is one of the most commonly used methods (98). Oxidation of As(III) to As(V) followed by As(V) adsorption is an effective arsenic elimination method because As(V) can be adsorbed onto solid surfaces more efficiently than As(III) (99, 100). Some examples of chemical oxidizing agents include ozone, chlorine, hydrogen peroxide, copper oxide, and potassium permanganate (101, 102). In addition, ultraviolet radiation in the presence of oxygen has also been demonstrated to increase As(III) oxidation due to the generation of hydroxyl radicals through photolysis of $FeOH_2^+$ (103, 104). Mn dioxide–polished sand has been shown to be an effective oxidant as well as adsorbent at low arsenic concentrations (100–300 ppb), but its oxidizing efficiency decreased at higher arsenic concentrations (700–1,000 ppb) (105). Recently, a new class of copper and Mn ternary metal oxide with nano-adsorbent has been developed for effective arsenic elimination (106). Nevertheless, the use of chemical oxidants can lead to higher Fe and Mn concentrations in drinking water as well as other byproducts such as trihalomethanes, which can counterbalance the effectiveness of using oxidants (107, 108).

As an alternative, biological oxidants such as *Gallionella ferruginea* and *Leptothrix ochracea*, also known as Fe- and Mn-oxidizing bacteria, have been shown to effectively remove arsenic in an eco-friendly way (109). Following As(III) oxidation, adsorption of As(V) using artificial adsorbents such as iron oxides can be easily performed in a cost- and environment-friendly manner. For example, hydrated ferric oxide (HFO) can bind strongly to As(V) due to its high surface area and inner surface complexation (110). One drawback is that the efficiency and reactivity of HFO can diminish over time due to its ability to form more crystalline Fe forms (111). To combat this, nanoscale Fe oxide particles with large surface area as well as Fe oxides with decorated functional groups have been developed to enhance efficiency and dispersion (112, 113). While Fe oxides are cheap and can be reused, the use of this technology can release excess Fe into groundwater and clog filter material. As a possible alternative, highly porous zirconium dioxide (ZrO_2) nanoparticles designed with high adsorption capacity for both As(III) and As(V) can be employed. Moreover, the ability of ZrO_2 to bind As(III) allows for the elimination of the preceding oxidation step (114). Notably, the use of previously mentioned technologies such as HFO requires prior oxidation due to lower As(III)-binding efficiency, often by a factor of 100 compared to As(V) (115, 116). In addition, current mitigation programs are restricted to inorganic arsenic elimination. As mentioned previously, there is still much to learn about the toxicity, transport, environmental fate, and bioavailability of other arsenic species; therefore, in the future, it is imperative to design mitigation strategies based on specific needs and on characteristics of various arsenic species.

Most molecular, toxicological, and epidemiological studies have analyzed and depicted arsenic-related disease outcomes using drinking water and urinary arsenic concentrations as exposure standards. However, depending on the geographical area, dietary factors can contribute to a significant portion of a person's total arsenic exposure. In addition, while drinking water mainly contains inorganic arsenic, more than 100 organic arsenic species as well as inorganic arsenic have been detected in various types of foods, which may complicate the effects of chronic arsenic exposure (117). Using probabilistic exposure modeling, one study indicated that in the United States, food contributed 1.96 μg of daily inorganic arsenic intake, which is twice as much as the amount

contributed through drinking water (118). One of the most scrutinized food sources known to accumulate arsenic is rice, which is a dietary staple for half of the world's population. Traditional methods of cultivating rice involve paddy field flooding, which controls for weeds and promotes mobilization of important nutrients such as Fe and zinc but also subjects the plants to highly arsenic-contaminated irrigation water. However, constant flooding is not a requirement for growing rice plants. In fact, plants grown under aerobic soil conditions for a part or a whole growing season have been shown to retain significantly less arsenic in the grains (119–121). While this water-conservative method is simple and effective, shortcomings include lower rice yields and the accumulation of cadmium, which is another highly carcinogenic heavy metal (122). An alternative to differential irrigation methods is the application of soil amendments, which involves adding substances that reduce the bioavailability of arsenic in the plow layer (38). For example, Fe-based additives boost the availability of free Fe oxide in the soil, thereby reducing the release of arsenite into the soil. Furthermore, silicon-containing fertilizer has been shown to share a similar uptake pathway as arsenic, while Mn oxide additives can effectively reduce arsenic uptake through diminishing arsenic mobilization by catalyzing As(III) oxidation (123, 124). Other nonchemical additives, such as inoculating rice with algae, arsenic-oxidizing bacteria, microbial fuel cells, and yeast, have also been shown to be promising strategies (38, 125–127).

One of the main setbacks with the irrigation and soil amendment methods is the inability to completely block arsenic entry into the plants due to shared transport systems with essential nutrients. Thus, gene editing using molecular and traditional plant-breeding techniques may be employed to alter the inherent characteristics of plant growth by selecting for alternative phosphate transporters as well as low arsenic uptake and high arsenic-resistant characteristics. For example, overexpression of *Arabidopsis* ABC-type transporters allows plants to grow in highly toxic arsenic-contaminated conditions (128).

Despite the availability of a multitude of methods and techniques as well as immense efforts put into arsenic mitigation, several key challenges still persist. To name a few, inadequate planning for region-specific arsenic mitigation strategies, lack of coordination between different stakeholders, adaptation to old water-extraction methods, poor work quality, and unaffordability of sophisticated treatment technologies in developing countries have all played a role in overshadowing effective mitigation measures (129). In Bangladesh alone, between 2002 and 2009, hundreds of millions of US dollars donated through the United Nations Development Program, WHO, UNICEF, UN Foundation, and international development agencies of the United States, Japan, Sweden, Britain, the Netherlands, Switzerland, and Denmark have been spent on remediation efforts (94). However, the lack of long-term follow-up and timely evaluation impeded mitigation efforts, and little success was found after most projects' first year of implementation. The lack of positive feedback can certainly thwart donor interest and overshadow past achievements. In response to a shortage of funding and lack of central water governance, decentralized community-based treatment systems have emerged in South and Southeast Asia (130). The novelty of these systems is reflected by their market-based approach, where each step of the mitigation program is compensated and accounted for. Specifically, each participating family in the treatment program, which serves approximately 100–200 families, is considered a stakeholder and required to pay a monthly fee to cover maintenance and operational costs of the water mitigation plant. Operators of the plant as well as water delivery personnel are also compensated for their work. The interdependence of this system not only stimulates local employment but also ensures quality control (130). However, this system may only be effective for communities that are economically well off. Those that are economically strained will still be vulnerable; thus, new strategies are needed to bring effective mitigation methods to poverty-stricken areas.

CONCLUSION

This review provides an expansive and up-to-date discussion of arsenic-related challenges and opportunities facing the global community. Despite substantial research and development efforts, millions of people are still exposed to unsafe amounts of arsenic through inhalation, diet, and/or drinking water. Due to both the pervasive presence and the seriousness and extent of arsenic-related health effects, collected efforts from multiple stakeholders are necessary: These include individuals, educators, researchers, policy-makers, and government leaders. It may be necessary to move from individualized traditional approaches into an integration of efforts from varied sides, which may provide opportunities to coalesce and tackle old issues with new strategies. Notably, the use of technology and computer modeling systems may become an indispensable part of future research and mitigation methods to deal with global arsenic contamination.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This work was supported by NIH grants ES000260, ES022935, ES023174, and ES026138.

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Erratum >