The Broad Scope of Health Effects from Chronic Arsenic Exposure: Update on a Worldwide Public Health Problem

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Background: Concerns for arsenic exposure are not limited to toxic waste sites and massive poisoning events. Chronic exposure continues to be a major public health problem worldwide, affecting hundreds of millions of persons.

Objectives: We reviewed recent information on worldwide concerns for arsenic exposures and public health to heighten awareness of the current scope of arsenic exposure and health outcomes and the importance of reducing exposure, particularly during pregnancy and early life.

Methods: We synthesized the large body of current research pertaining to arsenic exposure and health outcomes with an emphasis on recent publications.

Discussion: Locations of high arsenic exposure via drinking water span from Bangladesh, Chile, and Taiwan to the United States. The U.S. Environmental Protection Agency maximum contaminant level (MCL) in drinking water is 10 µg/L; however, concentrations of > 3,000 µg/L have been found in wells in the United States. In addition, exposure through diet is of growing concern. Knowledge of the scope of arsenic-associated health effects has broadened; arsenic leaves essentially no bodily system untouched. Arsenic is a known carcinogen associated with skin, lung, bladder, kidney, and liver cancer. Dermatological, developmental, neurological, respiratory, cardiovascular, immunological, and endocrine effects are also evident. Most remarkably, early-life exposure may be related to increased risks for several types of cancer and other diseases during adulthood.

Conclusions: These data call for heightened awareness of arsenic-related pathologies in broader contexts than previously perceived. Testing foods and drinking water for arsenic, including individual private wells, should be a top priority to reduce exposure, particularly for pregnant women and children, given the potential for life-long effects of developmental exposure.

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Ongoing exposures to toxic chemicals such as arsenic continue to pose a significant threat to public health. The World Health Organization (WHO) estimates that > 200 million persons worldwide might be chronically exposed to arsenic in drinking water at concentrations above the WHO safety standard of 10 µg/L (WHO 2008) (Table 1). Arsenic is a metalloid element that is encountered primarily as arsenical compounds. Within these compounds, arsenic occurs in different valence states, the most common of which are As^{III} (arsenites) and As^{V} (arsenates). Arsenic in drinking water is typically found in the inorganic form, either as As^{III} or As^{V}, whereas arsenic in food is found in the organic and inorganic forms, depending on the specific food [Agency for Toxic Substances and Disease Registry (ATSDR) 2007; European Food Safety Authority (EFSA) 2009] Sources of arsenic contamination include natural deposits as well as anthropogenic sources such as mining and electronics manufacturing processes and metal smelting (ATSDR 2007).

Arsenic holds the highest ranking on the current U.S. ATSDR 2011 substance priority list (ATSDR 2011b) (Table 2). ATSDR ranks chemicals using an algorithm that translates potential public health hazards into a points-scaled system based on the frequency of occurrence at National Priority List (NPL) Superfund sites as well as toxicity and potential for human exposure. Arsenic tops the list in spite of the fact that this ranking does not include full consideration of exposure from drinking water, diet, copper-chromated arsenic-treated wood, coal- and wood-burning stoves, arsenical pesticides, and homeopathic remedies (ATSDR 2007, 2011b; Akter et al. 2005; EFSA 2009; Rose et al. 2007). Therefore, the threat to human health posed by arsenic is even greater than its top ATSDR ranking would suggest. In regard to toxicity, the International Agency for Research on Cancer (IARC) defines arsenic as a Group I known human carcinogen that also induces a wide array of other noncancer effects, leaving essentially no bodily system free from potential harm (ATSDR 2007; IARC 2012; National Research Council 2001; WHO 2008).

Here we synthesize the large body of current research pertaining to arsenic exposure and health effects and emphasize the broadening scope of predicted and observed impacts of arsenic on public health. Understanding the wide range of these impacts drives home the importance of testing drinking-water sources and monitoring foods for arsenic. Whereas municipalities test public drinking-water sources, private wells can go untested. Recent data also raise concerns for arsenic exposure via foods including rice and organic brown rice syrup [Davis et al. 2012; EFSA 2009; Food and Drug Administration (FDA) 2012; Gilbert-Diamond et al. 2011; Jackson et al. 2012] as well as chicken feather meal products that are used in the human food system (Nachman et al. 2012).

Even as assessments of dietary exposure continue to unfold, drinking water remains a major concern for arsenic exposure. There are known, large-scale drinking-water contamination problems in countries such as Bangladesh (Ahsan et al. 2006; Argos et al. 2010, 2012; Smith et al. 2000b). However, chronic arsenic exposure is a concern in many parts of the world (Table 1). For example, arsenic concentrations in drinking water from some private wells in the United States are as high as 3,100 µg/L, which is in the range of the highest concentrations reported in Bangladesh (Nielsen et al. 2010; Yang et al. 2009). Yet detection of arsenic contamination even at these high levels remains problematic because it is tasteless, colorless, and odorless.

Given the large number of studies that address the broad range of information provided here, it is impractical to include all pertinent studies. Rather, we present a synthesis

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of information and cite recent studies that help illustrate the breadth and scope of the problems. When available, we cite current reviews that can serve as a resource for a more complete listing of relevant resources, most often focusing on single health issues such as cardiovascular disease (States et al. 2009). Detailed discussions of arsenic exposure and health effects can be found elsewhere (ATSDR 2007; EFSA 2009; Gibb et al. 2011; States et al. 2011).

As awareness of arsenic exposure increases, so should knowledge of its health effects because the impact of chronic arsenic exposure on public health is substantial. In addition to skin lesions and skin cancer (ATSDR 2011a; Sengupta et al. 2008; Smith et al. 2000a), neurological, respiratory, cardiovascular, and developmental effects and more are linked to chronic arsenic exposure (Table 3) (Argos et al. 2012; Smith and Steinmaus 2009; States et al. 2011). Acute poisonings still occur but are uncommon (Bronstein et al. 2011). Arsenic renders its toxicity via numerous mechanisms: Arsenic is genotoxic and has multiple effects on cellular signaling, cellular proliferation, DNA structure, epigenetic regulation, and apoptosis (Flora 2011; Ren et al. 2011; States et al. 2011).

A wealth of data comes from ongoing epidemiological studies of large populations exposed to a wide range of arsenic levels in drinking water in regions such as Taiwan, Bangladesh, Chile, India, and Argentina (Ahsan et al. 2006; Argos et al. 2012; Chen CL et al. 2010a; Smith et al. 2011; Yuan et al. 2010). In Taiwan, a stable population in an arsenic-endemic region had been exposed to arsenic via drinking water since the 1900s [Chen CJ et al. 1988b, 1992; Gibb et al. 2011; Tseng 1977; U.S. Environmental Protection Agency (EPA) 2001; Wu et al. 1989]. In Bangladesh, tube wells were dug in the 1970s as a source of drinking water to avoid microbial contamination, only to later learn that the tube wells are contaminated with naturally occurring arsenic (Smith et al. 2000b). Researchers established a cohort in Bangladesh with over 10,000 persons enrolled as part of the Health Effects of Arsenic Longitudinal Study (HEALS) (Ahsan et al. 2006; Argos et al. 2012). Researchers are also studying a population in Chile where some cities were exposed to high concentrations of arsenic for a defined, limited period of time (1958–1971), at which point, systems were installed to remove arsenic from drinking water (Biggs et al. 1998). This population is particularly well suited for studies related to latency periods for chronic diseases and susceptibility during development (Dauphine et al. 2011; Liaw et al. 2008; Marshall et al. 2007; Yuan et al. 2010). Major findings from these cohorts and other studies are described in the following sections.

In light of accumulated research, there is increasing awareness that arsenic exposure might be affecting more persons and contributing to more chronic disease than previously thought. In the HEALS cohort, approximately 21.4% of all deaths and 23.5% of deaths associated with chronic disease could be attributed to arsenic at > 10 μg/L in drinking water (Argos et al. 2010). Here we present an overview and synthesis of recent information on worldwide concerns for arsenic exposures and public health. The enormity of potential public health impacts is striking. Given this potential, testing and remediating arsenic in drinking water at the level of single private wells and reducing dietary exposure are critical to protecting public health.

Worldwide Concerns for Arsenic Exposure

Arsenic exposure is a major environmental public health concern worldwide and a primary concern for exposure is via drinking water (Table 1). The WHO and Australia set or confirmed a guideline level of 10 μg/L for arsenic in drinking water in 2008 and 2011, respectively (National Health and Medical Research Council 2011; WHO 2008). The U.S. EPA promulgated that it lowered the maximum contaminant level (MCL) from 50 μg/L to 10 μg/L, effective in 2002 (U.S. EPA 2001). In many developing countries, including Bangladesh, 50 μg/L is still the commonly adopted guideline, primarily because of difficulties in remediating arsenic below that level (WHO 2008). The excess cancer risk associated with lifetime arsenic exposure at water concentrations of > 10 μg/L is approximately 1 in 300, which is 30–300 times higher than the cancer risks estimated for exposure to other known carcinogens in drinking water at concentrations equal to current U.S. drinking-water standards (Smith et al. 2002).

What is the extent of chronic exposure via drinking water? The answer varies greatly depending on regional and local sources of arsenic (Table 1). For example, in Maine, the U.S. Geological Survey reported that 18.4% of wells tested had > 10 μg/L arsenic and estimated that 24,000–44,000 households might be affected (Nielsen et al. 2010). A recent study predicted that 42.7% of the area of aquifers in the southwestern United States has arsenic concentrations of ≥ 10 μg/L, although portions of these areas are in remote regions (Anning et al. 2012). Of 63,000 wells tested in North Carolina, 1,436 (2.3%) had arsenic concentrations of > 10 μg/L with a maximum of 806 μg/L (Sanders et al. 2012). In comparison, in Bangladesh in 1998, shortly after discovery of arsenic contamination, it was estimated that up to 94% of tube wells in certain regions and 35% of all wells in the country contained > 50 μg/L arsenic (Smith et al. 2000b). In Chile, San Pedro de Atacama drew most of its public drinking water from the Vilama River, which contained approximately 600–680 μg/L arsenic, and some homes with

Table 1. Arsenic exposure concerns worldwide.

Country	Estimated exposed population (millions)[a]	Arsenic concentration in drinking water (μg/L)	References
Argentina	2.0	< 1 to 7,550	Bates et al. 2004; Moore et al. 2004; Steinmaus et al. 2010
Bangladesh	35–77	< 10 to > 2,500	Kinniburgh and Smedley 2001
Chile[b]	0.4	600 to 800	Ferreccio et al. 2000; Smith et al. 1998, 2000a
China	0.5–2.0	< 50 to 4,400	Yu et al. 2007
Ghana	< 0.1	< 2 to 175	Asante et al. 2007; Smedley 1996
India	> 1.0	< 10 to > 800	Acharyya et al. 1999
Mexico	0.4	5 to 43	Calderón et al. 2001; Camacho et al. 2011; Meza et al. 2004, 2005
Taiwan	NA	< 1 to > 3,000	Chen et al. 2010a, 2010b
United States	> 3.0	< 1 to > 3,100	Anning et al. 2012; Ayotte et al. 2003; Burgess et al. 2007; Nielsen et al. 2010; NRDC 2000; Peters 2008; Sanders et al. 2012; Thundiyil et al. 2007; Xue et al. 2010
Vietnam	> 3.0	< 0.1 to 810	Winkel et al. 2011

Abbreviations: NA, not available; NRDC, National Resources Defense Council.
[a]Estimated number of persons exposed to > 10 μg/L arsenic in drinking water. Estimates were obtained from cited references and usually refer to a specific city or region within each country. The actual number of exposed persons in each country could be higher. [b]The population in one region of Chile was exposed to high levels of arsenic from 1958 to 1971, and studies of long-term and latent effects are ongoing.

Table 2. The ATSDR 2011 substance priority list.

Rank	Substance name	Points	CAS number
1	Arsenic	1665.5	007440-38-2
2	Lead	1529.1	007439-92-1
3	Mercury	1460.9	007439-97-6
4	Vinyl chloride	1361.1	000075-01-4
5	Polychlorinated biphenyls (PCBs)	1344.1	001336-36-3
6	Benzene	1332.0	000071-43-2
7	Cadmium	1318.7	007440-43-9
8	Polycyclic aromatic hydrocarbons	1282.3	130498-29-2
9	Benzo[*a*]pyrene	1305.7	000050-32-8
10	Benzo[*b*]fluoranthene	1252.4	000205-99-2

This list was generated by the ATSDR (2011) using an algorithm that translates potential public health hazards into a points-scaled system based on the frequency of occurrence at NPL Superfund sites and on toxicity and potential for human exposure.

no public supply drew water from the San Pedro River, which contained 170 µg/L; in contrast, a town 40 km away had an average drinking-water arsenic concentration of 15 µg/L (Hopenhayn-Rich et al. 1996).

Testing is required to determine whether a given source of drinking water has high levels of arsenic. Even if the local municipality does not test private wells for arsenic, test kits are available worldwide through local municipalities, public health offices, and commercial sources accessible via the Internet (Water Quality Association 2012; Massachusetts Department of Environmental Protection 2011). Hot spots of arsenic contamination of drinking-water sources can occur because of proximity to naturally occurring arsenic found in certain types of bedrock and sediments as well as proximity to hazardous waste sites. Therefore, drinking-water sources with high arsenic concentrations can exist in very close proximity to sources with low arsenic concentrations, with differences noted even in neighboring individual wells.

Another source of growing concern for arsenic exposure is through diet. For persons with limited exposure to arsenic via drinking water, diet is the major source of exposure (EFSA 2009). Rice, organic rice syrup, fruits, juices, and other grains can contain significant amounts of arsenic (FDA 2012; Jackson et al. 2012; Norton et al. 2012). Furthermore, rice consumption has been shown to be associated with urinary arsenic levels in pregnant women and children (Davis et al. 2012; Gilbert-Diamond et al. 2011). Because of their level of consumption of rice products, children < 3 years of age are estimated to have the greatest exposures to arsenic via diet (EFSA 2009).

Health Outcomes of Arsenic Exposure

Dermatological effects. Cutaneous lesions are one of the best-known clinical manifestations of chronic arsenic exposure and can occur within months or after several years of exposure (Das and Sengupta 2008; WHO 2005). Clinical photos of different types of arsenic-associated lesions are shown in Figure 1. Melanosis (hyperpigmentation) is considered an early and more common manifestation (Figure 1A), whereas keratosis (Figure 1B) is considered a sensitive marker of more advanced stages of arsenicosis (Das and Sengupta 2008; Sengupta et al. 2008). Leucomelanosis (hypopigmentation) also occurs but less frequently than melanosis or keratosis. Arsenic-related melanosis can be diffuse or patchy, or exhibit a distinctive "rain drop" pattern, and these lesions often appear on the trunk of the body. Keratotic lesions tend to appear mainly on the palms and soles. Sudden increases in the size of keratotic lesions, or cracks or bleeding of lesions, suggest malignant transformation—often to squamous cell carcinoma (Figure 1C,D). Analyses of numerous epidemiological studies of skin lesions suggest that most persons with skin lesions had consumed water with arsenic concentrations of > 100 µg/L, although lesions have been reported at arsenic concentrations of < 50 µg/L (Argos et al. 2011; Smith and Steinmaus 2009). Nutritional, economic, and smoking status are contributing factors for susceptibility to skin lesions as are sex and age, with a greater prevalence of skin lesions in older men (Pierce et al. 2010). A recent report from the HEALS prospective study found that the risk of skin lesions did not decrease after reducing exposure for up to several years (Argos et al. 2011). Therefore, lesions can appear several years after exposure diminishes. The vast majority of exposed individuals (even with high levels of chronic exposure) will not develop skin lesions but are still at risk of arsenic-related skin and internal cancers and other noncancer diseases (Argos et al. 2010; Chen Y et al. 2011; Parvez et al. 2010).

Arsenic exposure and cancer. Arsenic is a known carcinogen in skin, lung, bladder, liver, and kidney, with evidence suggesting lung cancer is the most common cause of arsenic-related mortality (IARC 2012; National Toxicology Program 2011). Skin cancer has long been associated with chronic arsenic exposure (ATSDR 2007; Yu et al. 2006). Squamous cell carcinoma *in situ* (Bowen's disease; Figure 1C), invasive squamous cell carcinoma (Figure 1D), and basal cell carcinoma (Figure 1E) are the most common types of skin cancer associated with chronic arsenic exposure. Studies from arsenic-endemic regions of Taiwan revealed that the overall prevalence of skin cancer was 10.6 per 1,000 persons and was associated with increased arsenic drinking-water concentrations (Tseng 1977) and increased urinary concentrations of certain arsenic metabolites (Tseng 2007). In the United States, where arsenic exposure is generally lower, significantly increased risks for squamous cell and

Table 3. Arsenic affects a broad range of organs and systems.

Targets	Health effects	References
Skin	Skin lesions	Argos et al. 2011; Haque et al. 2003; Smith et al. 2000a
	Skin cancer	Tseng 1977, 2007; Yu et al. 2006
Developmental processes	Increased infant mortality	Milton et al. 2005; Rahman et al. 2010a
	Reduced birth weight	Rahman et al. 2009
	Altered DNA methylation of tumor promoter regions in cord blood and maternal leukocytes	Intarasunanont et al. 2012; Kile et al. 2012
	Neurological impairments in children	Dong and Su 2009; Hamadani et al. 2011; Wasserman et al. 2004, 2007
	Early-life exposure associated with increased cancer risk as adults	Bates et al. 2004; Chen CL et al. 2010b; Liaw et al. 2008; Marshall et al. 2007; Su et al. 2011; Yuan et al. 2010
Nervous system	Impaired intellectual function in children and adults	Hamadani et al. 2011; Wasserman et al. 2004, 2007; Dong and Su 2009
	Impaired motor function	Gong et al. 2011; Parvez et al. 2011
	Neuropathy	Vahidnia et al. 2007
Respiratory system	Increased mortality from	
	Pulmonary tuberculosis	Smith et al. 2011
	Bronchiectasis	Smith et al. 2006
	Lung cancer	Heck et al. 2009; Marshall et al. 2007; Smith et al. 2009
Cardiovascular system	Coronary and ischemic heart disease	Chen Y et al. 2011; Gong and O'Bryant 2012
	Acute myocardial infarction	Yuan et al. 2007
	Hypertension	Abhyankar et al. 2012; Abir et al. 2012
Liver, kidney, and bladder	Liver cancer	Chen and Ahsan 2004; Chiu et al. 2004; Liaw et al. 2008; Liu and Waalkes 2008
	Kidney cancer	Bates et al. 2004; Yuan et al. 2010
	Bladder and other urinary cancers	Chen et al. 2010b; Chiou et al. 2001; Gibb et al. 2011; Marshall et al. 2007
Immune system	Altered immune-related gene expression and cytokine expression	Ahmed et al 2011; Andrew et al. 2008; Kile et al. 2012
	Inflammation	Ahmed et al. 2011
	Increased infant morbidity from infectious diseases	Rahman et al. 2010b; Spivey 2011
Endocrine system	Diabetes	Chen et al. 2007; Del Razo et al. 2011; Islam et al. 2012; Jovanovic et al. 2012
	Impaired glucose tolerance in pregnant women	Ettinger et al. 2009
	Disrupted thyroid hormone, retinoic acid, and glucocorticoid receptor pathways in mice and amphibians	Barr et al. 2009; Davey et al. 2007, 2008

The list of references is not intended to be comprehensive but rather to provide examples of health effects across multiple bodily systems.

basal cell carcinomas occurred in individuals in the top 97th percentile of toenail arsenic concentrations (Karagas et al. 2001), particularly among individuals carrying susceptible genotypes for the nucleotide excision repair genes (Applebaum et al. 2007).

Chronic arsenic exposure is also associated with an increased risk of lung cancer (IARC 2012). In the Chilean cohort that was exposed to high arsenic concentrations in drinking water (> 850 µg/L) for a limited period of time (1958–1971), the peak mortality rate ratio (MRR) for lung cancer was highest at 3.61 (95% CI: 3.13, 4.16) for men in 1992–1994 (Table 4), suggesting a 34- to 36-year latency period (Marshall et al. 2007). Arsenic is carcinogenic in the lung regardless of oral or inhalation pathways of exposure, and it is well established that lung cancer is associated with exposure to > 100 µg/L arsenic in drinking water. However, it is unclear whether such an association exists for exposure to < 100 µg/L arsenic (Chen CL et al. 2010a; Heck et al. 2009; Putila and Guo 2011; Smith et al. 2009; Steinmaus et al. 2010).

Increasing evidence supports the hypothesis that arsenic exposure can increase cancer risks in other organs. Increased risk of bladder cancer is significantly associated with increasing arsenic exposure, particularly with longer exposure periods (> 40 years) and higher drinking-water concentrations (> 600 µg/L) (Chen CJ et al. 1992; Chen CL et al. 2010b; Chiou et al. 2001; Gibb et al. 2011; Marshall et al. 2007). For kidney cancer, mortality rates increased in a dose-dependent manner for drinking-water concentrations ranging from 170 to 800 µg/L in Taiwan (Chen CJ et al. 1988a); the MRRs at 800 µg/L were 196 for men and 37.0 for women. Results from other studies in Taiwan support this finding (Smith et al. 1992). More studies with larger sample sizes are warranted to evaluate associations at drinking-water concentrations of < 100 µg/L.

A causal association between arsenic exposure and liver cancer, particularly liver angiosarcoma, was suspected as early as 1957, and several studies have substantiated that suspicion (e.g., Liaw et al. 2008; Smith et al. 1992). A number of studies from the Taiwan cohort have demonstrated increases in liver cancer deaths with increasing concentrations of arsenic in drinking water. For example, a significant dose-dependent linear trend in MRRs for liver cancer was reported with increasing arsenic concentrations in drinking water ranging from 170 to 800 µg/L (Chen CJ et al. 1988a; Wu et al. 1989). Links between arsenic exposure and liver cancer have also been supported by other reports (Chen CL et al. 2010b; Chen and Ahsan 2004; Chiu et al. 2004; Liaw et al. 2008; Morales et al. 2000). Taking epidemiological, rodent, and *in vitro* studies together, the evidence shows that the liver is a target organ of arsenic carcinogenicity (Liu and Waalkes 2008).

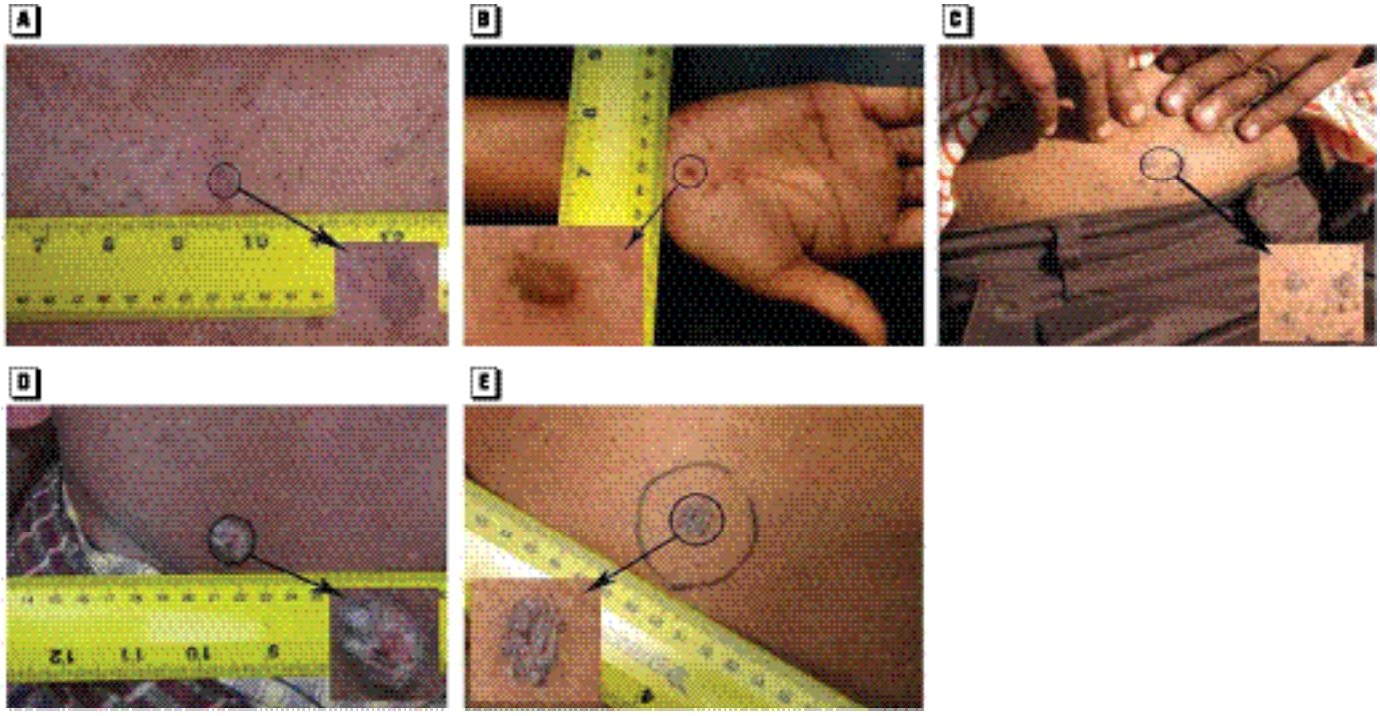

Figure 1. Skin manifestations of chronic arsenic exposure. (*A*) Hyperpigmentation (melanosis); (*B*) hyperkeratosis (keratosis); (*C*) squamous cell carcinoma *in situ* (Bowen's disease); (*D*) invasive squamous cell carcinoma; and (*E*) basal cell cancer.

Table 4. Peak mortality ratios for internal cancers and bronchiectasis in Chilean cohort studies.

Disease	Reference	Peak mortality ratio (95% CI)	Type of mortality ratio	Subpopulation with peak ratio
Lung cancer	Marshall et al. 2007	3.61 (3.13, 4.16)	MRR	Men, 22–24 years after exposure reduction
Bladder cancer	Marshall et al. 2007	13.8 (7.74, 24.5)	MRR	Women, 22–24 years after exposure reduction
Childhood liver cancer	Liaw et al. 2008	14.1 (1.6, 126.2)	MRR	Girls born 1950–1957 (exposed during childhood), 0–19 years of age
Kidney cancer	Yuan et al. 2010	4.37 (2.98, 6.41)	MRR	Women, 21–25 years after exposure reduction
		9.52 (2.56, 24.4)	MRR	Women born 1950–1970 (exposed *in utero* and during childhood), 21–25 years after exposure reduction
Bronchiectasis	Smith et al. 2006	50.1 (20.0, 103)	SMR	Women born 1958–1970 (exposed *in utero* and during childhood), 18–29 years after exposure reduction

Abbreviations: MRR, mortality rate ratio; SMR, standardized mortality ratio. For the exposed group, arsenic concentrations in drinking water were high (about 870 µg/L) between 1958 and 1970, at which point, filtration systems were installed thereby lowering the arsenic exposure. At the time of exposure reduction, the exposed population ages ranged from prenatal through adulthood.

Other effects on multiple bodily systems. A multitude of other health effects are linked to chronic arsenic exposure. These arsenic-associated health problems affect nearly every major organ and organ system in the body (Table 3). A comprehensive review of the literature for these effects is beyond the scope of this review; therefore, this section addresses the broad range of harmful effects of arsenic in the human body and makes apparent the impact of arsenic-contaminated drinking water on public health. Taken together, the body of data drives home the critical importance of monitoring for arsenic in food sources and drinking-water sources, including private wells.

Significant neurological impairments are evident in children and adults who exhibit impaired cognitive abilities and motor functions after arsenic exposure (Chen Y et al. 2009; Dong and Su 2009; Gong et al. 2011; Hamadani et al. 2011; Parvez et al. 2011; Vahidnia et al. 2007; Wasserman et al. 2004, 2007). Cognitive impairments were observed in children at 6 and 10 years of age (Wasserman et al. 2004, 2007). One recent study reported impairments in verbal and full-scale IQ in girls but not boys (Hamadani et al. 2011). In adults, arsenic exposure in drinking water is linked to significantly lower scores on tests of cognitive ability as well as lower education levels (Gong et al. 2011). Peripheral neuropathy and painful muscle spasms are also known to occur with arsenic exposure (Sengupta et al. 2008; Vahidnia et al. 2007).

In addition to lung cancer, chronic arsenic exposure is associated with other respiratory system effects. Mortality from pulmonary tuberculosis was increased in arsenic-exposed individuals in the Chilean cohort (Smith et al. 2011). In the same cohort, increased mortality from bronchiectasis was significant for those exposed to arsenic during early life with a standardized mortality ratio (SMR) of 50.1 (Table 4) (Smith et al. 2006). Reduced forced expiratory volume and forced vital capacity is associated with early-life exposure to arsenic, with a magnitude of reduction similar to smoking throughout adulthood (Dauphine et al. 2011). Other respiratory symptoms include chronic cough, blood in the sputum, and other breathing problems (Parvez et al. 2010).

The cardiovascular system is affected in several ways by arsenic (Abhyankar et al. 2012; Chen Y et al. 2009, 2011; States et al. 2009; Yuan et al. 2007). Cardiovascular effects include carotid atherosclerosis (Huang et al. 2009) and ischemic heart disease (Abhyankar et al. 2012; Chen Y et al. 2011; States et al. 2009). Furthermore, an association between hypertension and arsenic exposure is evident in some studies, and additional larger studies are needed to substantiate the link (Abhyankar et al. 2012; Abir et al. 2012).

Immune system effects of arsenic exposure are evident in several contexts. Effects include altered immune-related gene expression and cytokine production in lymphocytes (Andrew et al. 2008; Morzadec et al. 2012) and in lung (Lantz et al. 2007). Arsenic is significantly associated with increased infant morbidity from infectious diseases (Rahman et al. 2010b). Furthermore, maternal urinary arsenic during pregnancy is significantly associated with increased inflammation and reduced numbers of T cells as well as altered cytokine profiles in cord blood (Ahmed et al. 2011) and reduced thymic function in infants (Ahmed et al. 2012).

Multiple endocrine effects of arsenic exposure are suggested from studies in human and animal studies. These include affecting hormone regulation via the retinoic acid, thyroid hormone, and estrogen receptors (Barr et al. 2009; Davey et al. 2007, 2008; Ettinger et al. 2009; Smith and Steinmaus 2009; Watson and Yager 2007). Increased occurrence of diabetes is also linked to arsenic exposure, particularly at higher doses and with exposure periods of > 10 years (Chen CJ et al. 2007; Del Razo et al. 2011; Islam et al. 2012; Jovanovic et al. 2012).

Varied Susceptibilities

Genetic and nutritional factors in susceptibility. The variety of biological systems often simultaneously affected by arsenic is further complicated by varied individual susceptibilities to its toxic effects. For example, inter-individual variation in the ability to methylate arsenic is associated with differential susceptibility to the effects of arsenic exposure (Hall and Gamble 2012; Steinmaus et al. 2010). Genetic polymorphisms have also been shown to be a contributing factor (Agusa et al. 2012; Ahsan et al. 2007; Applebaum et al. 2007; Argos et al. 2012; Pierce et al. 2012; Porter et al. 2010; Reichard and Puga 2010). A recent large, comprehensive genome-wide association study identified specific genetic variations associated with risk for skin lesions as well as differences in arsenic metabolism (Pierce et al. 2012). Evidence is also building that nutritional factors, notably folate, appear to play an important role in arsenic methylation and elimination (Basu et al. 2011; Chen Y et al. 2009; Gamble et al. 2007; Hall and Gamble 2012; Pilsner et al. 2009). For example, low folate and hyperhomocysteinemia are associated with increased risk of skin lesions (Pilsner et al. 2009). Together, current information about arsenic metabolism across individuals sheds light on possibilities for new strategies for the prevention and amelioration of the toxicity of arsenic.

Susceptibility during development and long-term latency. Adverse pregnancy and developmental outcomes are associated with early-life exposure to arsenic (Vahter 2008). Arsenic exposure is significantly associated with increased infant mortality and, in some studies, increased spontaneous abortion and stillbirth (Milton et al. 2005; Rahman et al. 2010a; von Ehrenstein et al. 2006) as well as reduced birth weight (Rahman et al. 2009). Early-life arsenic exposure is also associated with neurological impairments in children (Hamadani et al. 2011; Parvez et al. 2011; Wasserman et al. 2004, 2007). For example, motor function in children, as well as verbal and full-scale IQ in girls, are both inversely associated with arsenic exposure (Hamadani et al. 2011; Parvez et al. 2011). Prenatal exposure also affects the developing immune system. Maternal urinary arsenic concentrations are associated with increased inflammation as well as altered cytokine profiles in cord blood and reduced thymus size and function in newborns (Ahmed et al. 2011, 2012). Altered immune responses are consistent with the observation of increased risk for lower respiratory infections and diarrhea in infants with increasing arsenic exposure (Rahman et al. 2010b).

The impacts of early-life arsenic exposure can continue into adulthood (Vahter 2008). Exposure during pregnancy and childhood is associated with an increased occurrence and/or severity of lung disease, cardiovascular disease, and cancer in childhood and later in life, with evidence of decades-long latency periods for these health conditions (Table 4) (Dauphine et al. 2011; Liaw et al. 2008; Marshall et al. 2007; Smith et al. 2011; Yuan et al. 2010). Childhood liver cancer MRRs were 9–14 times higher for those exposed as young children as compared with controls (Liaw et al. 2008). Other reports of latency periods extending over 50 years include skin cancer (Haque et al. 2003), urinary cancers (Bates et al. 2004; Chen CL et al. 2010b; Marshall et al. 2007; Su et al. 2011), and lung cancer (Marshall et al. 2007; Su et al. 2011). For example, peak SMRs for childhood liver cancer and bronchiectasis were 14.1 and 50.1 times higher, respectively, for individuals exposed to arsenic *in utero* and during childhood as compared with individuals exposed during other periods of their lives (Table 4) (Smith et al. 2006). Bladder cancer mortality peaked 25–36 years from the initiation of exposure (Marshall et al. 2007), and kidney cancer MRR peaked 21–25 years from initiation of exposure and was highest for women (Yuan et al. 2010). Regarding noncancer health effects, early-life arsenic exposure is associated with increased adult mortality from pulmonary tuberculosis (Smith et al. 2011), bronchiectasis (Smith et al. 2006), and myocardial infarction (Yuan et al. 2007).

Together the data indicate a sensitivity during development to health effects that can be long lasting and latent for > 50 years. The

implications are profound and make it clear that every effort should be made to prevent exposure of pregnant women, women of childbearing age, infants, and children to arsenic in order to prevent a multitude of health effects, particularly cancer, later in life.

Conclusions

Environmental health issues are not limited to toxic waste sites and poisoning events: some deleterious exposures come from naturally occurring substances, such as arsenic often found in drinking water. Arsenic affects multiple biological systems, sometimes years or decades after exposure reductions. Studies that reveal the complex nature of the origins and toxicity of arsenic highlight the importance of heightened awareness of arsenic-related health effects in broader contexts than previously perceived. In spite of current efforts, over 200 million persons globally are at risk of arsenic exposure at levels of concern for human health. Although specific regulatory levels might be debatable, all would agree that minimizing arsenic exposure is the best solution, especially prenatal and early-life exposure. Therefore, testing drinking water for arsenic is particularly important for pregnant women and women of childbearing age, given the potential for neurological and other lifelong effects of early-life exposure. The return on the investment can be substantial when measured in the reduced incidence of chronic disease and reduced rates of cancer worldwide.

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