

Arsenic in Drinking Water: Impact on Human Health

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In terms of its impact on human health, arsenic is unique in that most of the evidence linking it to diseases comes from epidemiological work; animal studies have not provided good models. It is also unique in causing a large number of different damaging effects and, as more studies are conducted, more such effects are found. To date, we know that arsenic from drinking water can cause severe skin diseases including skin cancer; lung, bladder, and kidney cancers, and perhaps other internal tumors; peripheral vascular disease; hypertension; and diabetes. It also seems to have a negative impact on reproductive processes (infant mortality and weight of newborn babies). The toxicology of arsenic involves mechanisms that are still not completely understood, but it is clear that a number of factors can affect both individual and population-level susceptibility to the toxic effects of arsenic-contaminated drinking water. Current research is addressing some of these, including genetic susceptibility and lifestyle factors that may increase arsenic's toxic effects, such as smoking, diet, and concurrent exposure to other substances. The reversibility of some effects upon cessation of exposure is also being investigated.

KEYWORDS: arsenic, health effects, drinking water, chronic exposure, arsenic metabolism

INTRODUCTION

The toxicological and human health effects caused by arsenic exposure were first described centuries ago, yet there are still many areas of inquiry that have not been elucidated, particularly with respect to the mechanisms of action of arsenic and the factors that may affect susceptibility to the damaging effects of this element and its compounds. These and other related areas are the topics of active research. Just in the last ten years, for example, there has been a plethora of publications focusing on these issues, including epidemiological studies investigating health outcomes in different populations across the globe exposed to arsenic in drinking water. Excellent comprehensive reviews have been published within the last few years by the International Program on Chemical Safety of the World Health Organization (IPCS 2001) and by the US National Research Council (NRC 1999, updated in 2001). The purpose of this article is to give a brief overview of these human studies.

Humans have been exposed chronically or over the long term to arsenic in occupational settings in mines, smelters, and wineries, and in the environment through dust, soil,

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and water. These exposures have resulted in the entry of arsenic into the body by skin contact, inhalation, and ingestion. The focus of this paper is on the health effects of arsenic on human populations, primarily from drinking water exposure. From the viewpoint of human health, arsenic can be considered a unique contaminant for at least four main reasons. First, effects can be measured in exposed populations, and risk estimates (and, consequently, acceptable regulatory standards) can be derived from environmentally relevant exposures. For many contaminants, risk assessments must rely on animal studies or extrapolations from very high occupational exposures. For arsenic, however, many epidemiological studies have consistently demonstrated health effects, in some cases showing dose-response patterns, within the range of realistic human exposure levels. Second, there are no definitive animal models to represent the effects caused by arsenic in humans. This is due, in part, to the fact that the metabolism and toxicity of arsenic in humans is very different from that in most animal models used in laboratory-based sciences. Third, arsenic is associated with increased risks for a wide range of diseases. To date, it has been linked to high risks of several types of cancers, as well as of diabetes, vascular disease, hypertension, neurological disorders, reproductive problems, and the well-known skin damage. And new effects continue to be confirmed or suspected. Finally, exposure is a global phenomenon and, as noted elsewhere in this issue, new exposed populations are constantly being discovered. So, although arsenic exposure is an old problem, it is also a current one.

EARLY REPORTS OF HEALTH EFFECTS

Descriptions of dermatological effects caused by arsenic ingestion, including hyperkeratoses, alterations in pigmentation, and skin cancer, date back over 100 years. Cases of lung cancer from occupational exposure to arsenic were described in the 1940s (IPCS 2001). Some landmark observations of the association between arsenic ingestion via drinking water and health effects are described below.

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In Argentina, the effects of arsenic were first reported in 1917 by Astolfi, and the term “Bell Ville Disease” was coined to describe frequent skin disorders found among residents of a town by that name in the province of Córdoba (detailed in Hopenhayn-Rich et al. 1996). Most case studies were based upon observations by local dermatologists, and the characteristic “arsenicosis” led to the term “HACRE”—Hidroarsenicismo Crónico Regional Endémico (Regional Endemic Chronic Hydroarsenicism)—reported in many Argentinian scientific journal articles and illustrated in FIGURE 1. The source of the arsenic exposure resided in deep water wells, found in individual homes and farms or in the centers of small towns.



FIGURE 1 Patients from Córdoba, Argentina, with skin keratoses, amputations, and skin cancer. PHOTOGRAPHS COURTESY OF DR ENRIQUE TELLO.

In areas of southwestern Taiwan, villages changed from surface water to groundwater or artesian wells in the 1920s to improve the microbiological quality of drinking water (NRC 1999). This led to unexpected and widespread water contamination by naturally occurring arsenic. A peripheral vascular disease that can lead to gangrene of the extremities, known as Blackfoot Disease (BFD), was first described in the 1920s in areas of southwestern Taiwan (IPCS 2001) (SEE FIG. 2). Since then, the prevalence of BFD has increased, and its association with arsenic in artesian well water has been thoroughly characterized. In addition, BFD-affected individuals commonly display arsenic-induced skin disorders, further suggesting an association between arsenic exposure and BFD. However, BFD is mostly found in the Taiwanese arsenic-endemic area, and very rarely seen in other populations exposed to arsenic, leading some to believe that other factors may be making the population of this area particularly susceptible to BFD.

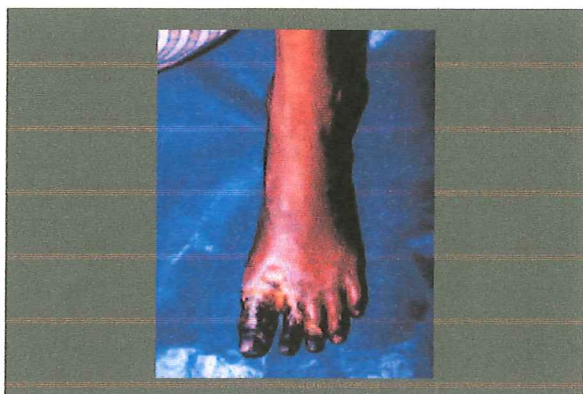


FIGURE 2 Patient with so-called “Blackfoot Disease.” PHOTO COURTESY DHAKA COMMUNITY HOSPITAL

The city of Antofagasta in northern Chile was the site of what can be termed a “natural experiment” in environmental epidemiology. The scarcity of water in the surrounding desert and the growing population led to a change in the water source for the city in 1958. The Toconce River had sufficient flow to accommodate the growing demand. But unknown to the population, it also had very elevated arsenic concentrations, averaging around 800 µg/L (80 times higher than WHO’s recommended limit of 10 µg/L). Within a few years, signs of arsenic toxicity became apparent among local residents. By 1970, clinical reports of acute toxicity, skin disorders, and systemic damage led to the installation of an arsenic-removal plant that reduced the contamination significantly (Zaldivar 1974; Borgoño et al. 1977). However, health effects with long latencies, such as certain cancers, outlasted the exposure peak by decades. As a result, substantially higher than expected rates of bladder and lung cancer, for example, have been found in the population of the region (Smith et al. 1998; Ferreccio et al. 2000).

TOWARDS THE PRESENT

In the 1980s, several papers reported the results of epidemiological studies conducted in the arsenic-endemic areas of Taiwan. Not only did these investigations corroborate earlier findings linking arsenic to skin damage, but they also found clear dose-response relationships between arsenic levels in different localities and the risks of skin, bladder, lung, and kidney cancer mortality. These were the first rigorous population-based epidemiological studies showing a strong association between ingestion of arsenic-rich water and high risks of internal cancers (Chen et al. 1988; Wu et al. 1989). In fact, they suggested that arsenic could be one of the most significant environmental carcinogens, one affecting large numbers of people. These publications gave way to studies of cancer in other arsenic-affected populations and, subsequently, to investigations of other pathological conditions. They also opened the door for studies of exposed populations in other countries, including Finland, China, England, and Nicaragua. In addition, a great “epidemic” was uncovered in West Bengal and in Bangladesh, as described below (and elsewhere in this issue).

The initial cancer findings from Taiwan also gave rise to a number of questions relating to whether the results might be directly applicable to other populations exposed to high arsenic levels. These questions centered on three factors that could make the residents of the Taiwanese arsenic-endemic region more susceptible to the health effects of arsenic. Did they have an ethnic or genetic increased susceptibility to the toxicity of arsenic? Did their diet, reported to be poor in protein-rich foods, affect their capacity to detoxify arsenic? Did other constituents in the water act to intensify the damaging effects of arsenic?

These questions were first addressed directly by a study undertaken in Argentina, in the same area of Córdoba province discussed above (Hopenhayn-Rich et al. 1996, 1998). The residents of this area are predominantly Caucasians of European descent. They consume one of the largest amounts of beef per capita in the world and therefore have very high protein consumption (about twice that of citizens in the USA). Using a study design similar to that of the Taiwanese investigation, existing data sources were used to characterize past arsenic exposures and contemporary cancer mortality risks (1986–1991) from the major internal cancers found elevated in Taiwan, namely, bladder, lung, and kidney cancers. Although there were some limitations in reconstructing past exposure levels, the results were remarkably in accordance with those from

Taiwan. Subsequently, similar results were also found in Chile for the region of Antofagasta, in relation to a very high arsenic 12-year period (1958–1970) that resulted in bladder cancer risks over six times the national average for the period of analysis (1989–1993; Smith et al. 1998).

Currently, the World Health Organization, the US Environmental Protection Agency and other well-established health-protection organizations consider arsenic to be a skin, bladder, lung, and kidney carcinogen. Other target sites of arsenic are still under consideration. In addition to cancer, arsenic ingestion has been found to be associated with increased risks for a number of conditions related to the vascular system, such as peripheral vascular disease (PVD), hypertension, cerebrovascular disease (CVD), and coronary heart disease (CHD). Neurological effects and diabetes have also been found elevated in arsenic-exposed populations.

A more recently uncovered and very large “arsenic epidemic” has appeared in the West Bengal area of India and in neighboring Bangladesh (NRC 1999; Chowdhury 2000; IPCS 2001; see Charlet and Polya this issue). In these two adjacent regions, where millions of people have been exposed, the arsenic epidemic has been the unfortunate consequence of a well-intentioned change of water supply. The purpose of the change was to replace the microbiologically rich rivers and streams used as the primary source of water for bathing, drinking, and cooking and which caused innumerable cases of disease and death, particularly among young children. Thousands of shallow “tube” wells were dug, which were free of the viruses, bacteria, and parasites found in rivers, therefore providing much cleaner water for human consumption. However, nobody suspected that the wells might contain high concentrations of arsenic, and the “new” water did not undergo exhaustive chemical analyses. As in Antofagasta, Chile, it took several years for widespread evidence of arsenic poisoning to become apparent.

In the extensive endemic areas of India and Bangladesh, many people suffer from the overt skin lesions caused by arsenic, characterized by thick keratoses predominantly in the palms of the hands and soles of the feet. These make walking and manual activities very painful, and the skin cancers can metastasize to other parts of the body. FIGURES 3 AND 4 show some of the common external signs of arsenic toxicity, which are similar in various countries, including Argentina, China, Bangladesh, and India. It has been estimated that in Bangladesh alone, where about 80 million people are thought to have used the contaminated tube-well water, approximately 300,000 persons have arsenic-induced skin lesions and cancer (Chowdhury et al. 2000).



FIGURE 3 A patient from a village in Uttar Pradesh, India. PHOTO COURTESY OF D. CHAKRABORTI, SCHOOL OF ENVIRONMENTAL STUDIES, JADAVPUR UNIVERSITY, INDIA (WWW.SOESJU.ORG)



FIGURE 4 Some external signs of arsenic toxicity. PHOTOS COURTESY OF RICHARD WILSON, HARVARD UNIVERSITY, AND DHAKA COMMUNITY HOSPITAL

Reproductive and developmental effects, mediated through exposures during pregnancy, lactation, or early childhood, can have repercussions throughout a person's life. Surprisingly, although many studies of arsenic and cancer have been conducted, very little research has been undertaken on the potential for reproductive damage. In the last seven years, however, several investigations in Chile, Bangladesh, and Taiwan have reported increases in stillbirths, infant mortality, low birthweight, and prematurity (NRC 2001; Hopenhayn et al. 2003; Yang et al. 2003; Milton et al. 2005).

One of the greatest challenges for environmental epidemiology is to be able to detect effects at low exposure levels; difficulties are mostly due to methodologic limitations, particularly for studies of cancer or other long-latency effects. This, at least in part, explains the lack of strong or significant associations reported in recent studies of populations exposed to much lower arsenic levels (e.g. Steinmaus et al. 2003; Lamn et al. 2004) compared to the studies described above in Chile, Taiwan, India, and Bangladesh.

METABOLISM AND TOXICITY

The main forms of arsenic found in water used for human consumption and, to a lesser extent, in foodstuff are inorganic arsenic (In-As), occurring either as trivalent (As^{+3}) or pentavalent (As^{+5}) compounds. Other forms of arsenic, including organic compounds such as arsenobetaine or arsenocholine, are found in seafood. Sometimes these occur in relatively high concentrations, but they are much less toxic than the inorganic forms and are eliminated rapidly and unchanged through the urine. Ingested In-As is quickly absorbed from the gastrointestinal tract and passes through a series of steps while being metabolized through reduction reactions of pentavalent to trivalent arsenic forms, and methylation to monomethylarsonic acid (MMA) and then to dimethylarsinic acid (DMA). This methylation process has traditionally been considered as the detoxification pathway for In-As, resulting in the less toxic MMA and DMA species. Methylation also facilitates the excretion of In-As from the body. However, not all In-As is completely methylated to DMA, as can be shown by the presence of In-As as well as MMA and DMA in the urine; urination is the main route of elimination of ingested In-As in humans, accounting for approximately 70% of the intake. The average proportions of arsenic metabolites in urine are about 15–25% In-As, 10–15% MMA, and 70–80% DMA.

Methylation of In-As, as reflected by the relative concentrations of species (In-As, MMA, and DMA) in urine, varies widely among individuals and, to a lesser extent, among populations. It is also affected by factors such as gender (women are more efficient methylators, i.e. they have a

greater proportion of methylated species in urine), smoking (which lowers methylation efficiency), and ethnicity (some groups, such as native Andeans, appear to have increased capacity for methylation) (Vahter 2000). Other factors that also seem to play a role in methylation are protein consumption and availability of certain micronutrients, such as selenium and beta-carotene. A few studies have reported direct links between methylation ability and health outcomes, suggesting that individuals with lower methylation capacity are at increased risk of bladder cancer (Chen et al. 2003) and skin cancer (Yu et al. 2000).

In spite of the evidence linking urinary arsenic species distribution with a number of factors and risks, two major issues have recently surfaced that question the hypothesis that methylation capacity, as described by urine metabolites, is a direct marker of risk and susceptibility to the toxic effects of arsenic. First, it has been shown that in the process of methylation from MMA to DMA, a so-called "reduced MMA" (MMA^{+3}) is formed. MMA^{+3} is a highly reactive, toxic intermediate compound that could be responsible for the toxicity of arsenic (Vahter 2002). However, this has proved difficult to measure in epidemiological studies because it is quickly oxidized to MMA^{+5} and is difficult to preserve. Secondly, although urinary metabolites are used to assess exposure and susceptibility, it is still not clear what forms of arsenic remain in target tissues in the human body (NRC 2001).

EXPOSURE ASSESSMENT

In order to assess the health effects of arsenic, it is essential to assess exposure as accurately as possible. The methods of assessment, accordingly, depend on the source of exposure. In particular, the methods for environmental measurements of inhaled versus ingested arsenic focus on air and dust content versus water and food. However, since inhaled and ingested In-As biologically undergo the same metabolic pathway, human biomarkers of exposure for both routes of entry into the body are similar, such as in urine, blood, hair, and nails. In epidemiological studies of arsenic exposure through drinking water, the major exposure markers are the concentrations in the water sources and the sum of In-As, MMA, and DMA in urine (to differentiate from organic, much less toxic forms found in some seafood). Hair and nails are sometimes used, but external contamination cannot be separated from arsenic that is internally absorbed and ultimately deposited in hair or nails. An arsenic dose can be estimated by combining arsenic concentration in water with reported average daily water intake. Finally, duration of exposure or cumulative exposure is usually estimated, and some studies have used this factor to correlate with health effects (IPCS 2001).

MECHANISMS OF ACTION

Arsenic causes or increases the risk of numerous illnesses. Some of them have been repeatedly observed in different epidemiological investigations. Examples are skin damage including keratoses and skin cancer, internal cancers such as lung and bladder, and diseases of the vascular system. Other health problems, such as diabetes, cancers of other organs, and adverse reproductive outcomes have been observed, but the evidence is not yet conclusive, although it keeps increasing.

Given this large array of negative health endpoints, what are the underlying biological mechanisms by which arsenic causes or induces these effects? They have not been fully elucidated, but several mechanisms or modes of action are known to at least play a role. In terms of carcinogenicity, In-As does not directly cause genetic mutations that could

lead to cancerous cells, but instead appears to act indirectly by inducing chromosomal alterations, oxidative stress, cell proliferation, and inhibition of DNA repair (NRC 1999; Schoen et al. 2004). Some of these mechanisms, such as oxidative stress to cells, could account for some of the non-cancer negative health effects. Differences in the metabolism of In-As and the relative toxicities of methylated species, including some potentially highly reactive, albeit short-lived, species like MMA^{+3} could also exacerbate toxicity.

In the light of research findings from the last few years, some of the questions that are actively being investigated are as follows:

1. Are there specific individual or group characteristics that confer to some people higher susceptibility to the toxic effects of arsenic?
2. What are the effects of specific nutritional deficiencies of, for example, protein, selenium, or iron on the metabolism and toxicity of arsenic?
3. Are certain groups, such as pregnant women, infants and children, and immuno-compromised individuals, at higher risk to the toxic effects of arsenic?
4. Can the results from epidemiological studies at high exposure levels be linearly extrapolated to lower, more-widespread exposures (i.e. between 10 and 100 $\mu\text{g/L}$)?
5. Can exposure cessation prevent worsening or even lead to improvement of the dermatological conditions that are afflicting large populations?
6. What are the forms of arsenic that are most toxic to target tissues and organs?

MAGNITUDE OF THE PROBLEM: THE GLOBAL PERSPECTIVE

Arsenic is probably the environmental contaminant that is responsible for the highest risks of morbidity and mortality worldwide, both because of its toxicity and the number of people exposed. Unlike other chemical contaminants that are found in limited locations or only in restricted areas around a point source, dangerously high levels of arsenic have been identified in many water supplies around the world. Moreover, in some affected areas, such as in India, Bangladesh, Taiwan, and possibly China (Sun 2004), the sizes of the exposed populations are very large. Globally, many millions of people currently drink water containing unacceptably high arsenic levels, which are responsible for increases in a wide range of illnesses. In many countries, water supplies are still not routinely tested for arsenic, although as testing becomes more widespread, more and more locations of arsenic contamination are being discovered.

Finally, in some high-risk areas, we are probably only seeing the "tip of the iceberg." Several studies suggest that there is a long latency period between exposure to arsenic and the development of internal cancers, sometimes forty years or more. Since cancers and other diseases can take decades to appear, it is possible there will be a sharp increase in these diseases over the next few decades in areas of China, Bangladesh, and India. Here, high arsenic exposures are relatively recent, and the effects of arsenic are only now being more closely monitored.

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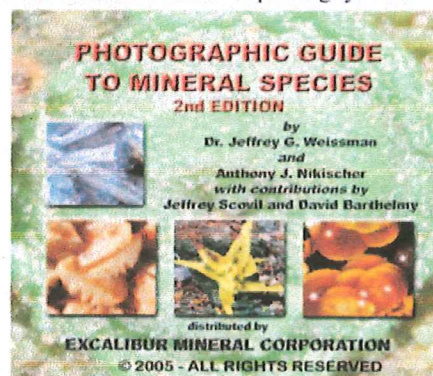
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