Environ Geochem Health (2009) 31:189–200
DOI 10.1007/s10653-008-9235-0

REVIEW PAPER

Chronic exposure of arsenic via drinking water and its adverse health impacts on humans

Mohammad Mahmudur Rahman · Jack C. Ng · Ravi Naidu

Received: 16 April 2008 / Accepted: 17 October 2008 / Published online: 4 February 2009

Abstract Worldwide chronic arsenic (As) toxicity has become a human health threat. Arsenic exposure to humans mainly occurs from the ingestion of As contaminated water and food. This communication presents a review of current research conducted on the adverse health effects on humans exposed to As-contaminated water. Chronic exposure of As via drinking water causes various types of skin lesions such as melanosis, leucomelanosis, and keratosis. Other manifestations include neurological effects, obstetric problems, high blood pressure, diabetes mellitus, diseases of the respiratory system and of blood vessels including cardiovascular, and cancers typically involving the skin, lung, and bladder. The skin seems to be quite susceptible to the effects of As. Arsenic-induced skin lesions seem to be the most common and initial symptoms of arsenicosis. More systematic studies are needed to determine the link between As exposure and its related cancer and noncancer end points.

Keywords Arsenic · Drinking water · Health effects · Arsenical skin lesions · Skin cancer · Internal cancers

M. M. Rahman · R. Naidu
Centre for Environmental Risk Assessment and Remediation (CERAR), University of South Australia, Mawson Lakes Campus, Mawson Lakes, SA 5095, Australia

M. M. Rahman · J. C. Ng · R. Naidu (✉)
Cooperative Research Centre for Contamination Assessment and Remediation of the Environment (CRC CARE), PO Box 486, Salisbury South, SA 5106, Australia
e-mail: ravi.naidu@crccare.com

J. C. Ng
National Research Centre for Environmental Toxicology, The University of Queensland, 39 Kessels Road, Coopers Plains, Brisbane, QLD 4108, Australia

Introduction

Inorganic As is ubiquitous in the environment and is a human carcinogen (IARC 2004). Chronic As toxicity in humans has been documented in many countries worldwide, particularly in countries of Southeast Asia. Significant As exposure mostly occurs through drinking As-contaminated water (WHO 2001; IARC 2004). Arsenicosis in many areas was triggered by the desire to obtain microorganism-free safe drinking water, and often surface water was inadvertently replaced by As-contaminated groundwater via the use of tubewells (Yoshida et al. 2004). The adverse health effects of As depend strongly on dose, duration of exposure, and the nutrition status of the exposed population. The clinical manifestations of As toxicity are many, but the most commonly observed symptoms in people who suffer from chronic As poisoning are the characteristic skin lesions. The main dermatological symptoms observed

in As affected people are melanosis (change of pigmentation) and keratosis (rough, dry, papular skin lesions). Chronic As exposure may also cause reproductive, neurological, cardiovascular, respiratory, hepatic, hematological, and diabetic effects in humans (WHO 2001). Intake of inorganic As was recognized as a cause of skin, bladder, and lung cancer (WHO 2001; IARC 2004). A number of articles have been published on chronic As exposure and its associated health effects (Morton and Dunnette 1994; Naqvi et al. 1994; Mandal and Suzuki 2002; Ng et al. 2003; Yoshida et al. 2004; Kapaj et al. 2006; Wang et al. 2007; Chen et al. 2007). Herein, the adverse health effects of As are reviewed.

Respiratory system

Ingestion of inorganic As for a prolonged period causes respiratory problems, including cough, chest sound, bronchitis, and shortness of breath (Guha Mazumder et al. 2000; Milton et al. 2001, 2003; Islam et al. 2007).

Guha Mazumder et al. (2000) examined the rate of respiratory signs and symptoms including cough, chest sounds, and shortness of breath and As exposure via drinking water in the population of the As-affected 24-South Parganas district of West Bengal in India. This study involved 7,683 participants of all ages ($\leq$9 to $\geq$60 years). The concentration of As in their drinking water ranged from <3 to 3,400 μg/l. It was reported that the prevalence odds ratio (POR) for cough were 5.0 and 7.8 for males and females, respectively; for chest sounds, the POR was 6.9 and 9.6, for males and females, respectively, after adjustment of age. For shortness of breath, the POR was 3.7 and 23.2 in males and females, respectively.

In a small cross-sectional study, Milton et al. (2001) investigated the link between As exposure and the rate of chronic bronchitis in Bangladesh based on 94 individuals (age range: 5 to >51 years) with arsenical skin lesions. Arsenic concentration in their drinking water ranged from 136 to 1,000 μg/l with a mean value of 614 μg/l. For exposed group, 14 of 40 males and 15 of 54 females were identified with the symptom of chronic bronchitis. For nonexposed group, 11 of 50 males and 2 of 74 females were identified.

Milton and Rahman (2002) conducted a study of respiratory effects among 169 subjects (44 exposed individuals with arsenical skin manifestations and 125 unexposed individuals) in Bangladesh. The range of As in drinking water for exposed subjects was 136–1,000 μg/l. The crude prevalence ratio for chronic bronchitis and chronic cough was 2.1 (95% confidence interval: 0.7–6.1). The prevalence ratio for chronic bronchitis increased with increasing As exposure. The relationship between As exposure and chronic cough and chronic bronchitis was also investigated among 136 subjects from three As-affected districts (Laxmipur, Barisal, and Madaripur) of Bangladesh (Milton et al. 2003). Based on their investigation, Milton et al. (2003) concluded that ingestion of inorganic As present in drinking water may lead to increased risk of chronic cough and bronchitis.

Recently Islam et al. (2007) studied the link between As exposure via drinking water and respiratory complications. They found high prevalence of respiratory complications such as breathing problems including chest sound, asthma, bronchitis, and cough in arsenicosis patients (125 subjects) of Bangladesh exposed to As-contaminated water (mean concentration of 216 μg/l) for more than 7 years.

Pulmonary system

Ingestion inorganic As through drinking water also causes pulmonary effects manifested by cough, chest sounds in the lung, and shortness of breath (Guha Mazumder et al. 2000; Mandal and Suzuki 2002). Based on a cohort study conducted from Antofagasta in Chile, Borgono et al. (1977) reported that 38.8% of 144 subjects with arsenical skin lesions complained of chronic cough, compared with 3.1% of 36 subjects without skin lesions. The study included 180 residents exposed to drinking water containing As at 800 μg/l. Guha Mazumder et al. (1997) reported that 89 (57%) of 156 subjects with arsenical skin lesions had complaint of cough, based on the study conducted from As-affected areas of West Bengal. Lung function tests were carried out on 17 patients. Of these, 53% of patients with skin lesions showed lung disease, and 41% had combined obstructive and restrictive diseases. More extensive investigation to characterize the nature of the pulmonary disease among arsenicosis patients is needed for further validation.

Cardiovascular system

Several epidemiological investigations have indicated the risk of hypertension and cardiovascular disease mortality due to As ingestion (NRC 1999, 2001). Increased prevalence of peripheral vascular disease has also been reported among residents with long-term As exposure from As present in drinking water in Taiwan, Chile, the USA, and Mexico (WHO 2001; NRC 1999, 2001; Wang et al. 2007; Chen et al. 2007).

A probable relation between low concentrations of As and risk of hypertension was observed in a study conducted from Michigan (Michigan Department of Public Health 1982; NRC 1999). Borgono et al. (1977) reported the prevalence of several manifestations of cardiovascular disease in 144 residents with arsenical skin lesions from Antofagasta, Chile compared with 36 residents without skin lesions. Engel and Smith (1994) reported the relationship between cardiovascular mortality and As exposure in 30 US counties where the average As concentration in drinking water was >5 μg/l.

Chiou et al. (1997) studied the link between cerebrovascular disease prevalence and human exposure to As from drinking water in Taiwan. Their investigation included 8,102 males and females from 3,901 households. They reported a significant relationship between As in drinking water and prevalence of cerebrovascular disease following adjustment for age, sex, hypertension, diabetes mellitus, smoking, and alcohol consumption. Chen et al. (1995) reported a possible connection between long-term exposure to As and prevalence of hypertension based on their examination of 382 men and 516 women residing in the blackfoot-disease-endemic villages of Taiwan. Prevalence of hypertension was 17.3% in males and 18.0% in females after adjustment for age. They suggested that long-term As exposure might induce hypertension in humans. Rahman et al. (1999a, b) also reported hypertension (assessed by blood pressure measurement) among 1,481 As-exposed residents compared with 114 unexposed residents in As-affected areas of Bangladesh.

Tseng et al. (1996) reported the relationship between previous As exposure and peripheral vascular disease after cessation of consumption of contaminated well water for more than two decades among 582 adults in the As-endemic villages in southwestern Taiwan. A significant dose–response relation was observed between prevalence of peripheral vascular disease and long-term As exposure after adjustment for age, gender, body mass index, cigarette smoking, and serum cholesterol and triglycerides levels. Tsai et al. (1999) investigated mortality from peripheral vascular disease in the As-endemic areas of Taiwan during 1971–1994 compared with local county and all of Taiwan. Significant excess mortality from peripheral vascular disease was reported for males and females compared with inhabitants in nonendemic areas of Taiwan. Yang (2006) examined the standardized mortality ratio of peripheral vascular disease among residents in the As-endemic areas in southwestern Taiwan from 1971 to 2003. The study showed that mortality due to peripheral vascular disease declined gradually for about 25–27 years after cessation of consumption of As-contaminated well water (Yang 2006).

Zierold et al. (2004) investigated As exposure and self-reported chronic diseases among 1,185 residents in Wisconsin using questionnaire interview. The range of As in water was from undetectable to 2,389 μg/l with a median of 2 μg/l. The study reported that the odds ratio of heart attack (95% confidence interval) was 2.1 for the group exposed to As above 10 μg/l compared with the group exposed to <2 μg/l of arsenic. In a cohort study, Lewis et al. (1999) investigated the relationship between exposure to As and mortality outcome in residents of Millard County, UT, who were exposed to drinking water containing median As ranging from 14 to 166 μg/l. Statistically significant increased mortality was observed for hypertensive cardiovascular disease and other heart diseases among cohort females. (Lewis et al. 1999; Wang et al. 2007)

Gastrointestinal system

With acute or subacute exposure, As could cause gastrointestinal problems (NRC 1999). Guha Mazumder et al. (1997) reported that only 3 of 156 cases had gastrointestinal hemorrhage due to portal hypertension, based on their study in As-impacted areas of West Bengal. Gross splenomegaly was not observed in most of the cases.

Hematological system

Anemia, leucopenia, and thrombocytopenia are common effects of chronic As toxicity (NRC 1999). Based

on their study from Niigata Prefecture of Japan, Terada et al. (1962) reported a pattern of anemia, leucopenia, and thrombocytopenia in 55 subjects who were exposed to As in drinking water. Harrington et al. (1978) examined complete blood counts of 184 subjects in the Ester Dome area of Alaska where average concentration of well water was 224 μg/l. No associations were observed between estimated daily As ingestion and any hematological abnormality.

Based on the study conducted from West Bengal, Guha Mazumder et al. (1997) reported that anemia was present in 47% of 156 patients with arsenical skin lesions. Hernandez-Zavala et al. (1999) studied urinary porphyrin excretion and erythrocyte heme synthesis pathway enzymes in the population of three towns in the Region Lagunera of Mexico. Mean As concentration in drinking water in towns varied from 14 to 300 μg/l. A dose-dependent increase in the ratio of urinary coproporphyrin III to coproporphyrin I and in the ratio of total coproporphyrin to total uroporphyrin was observed among the exposed groups (Hernandez-Zavala et al. 1999; NRC 2001).

Hepatic system

Guha Mazumder et al. (1988) reported hepatic damage in subjects residing in As-affected villages of West Bengal exposed to As-contaminated water (range 200–2000 μg/l). Overall prevalence of hepatomegaly was observed to be 92.6% in 67 people exposed to As at concentrations exceeding 50 μg/l. Prevalence however was much lower (6.2%) among people exposed to As less than 50 μg/l.

Hernandez-Zavala et al. (1998) studied liver function in subjects from three towns of Lagunera Region in Mexico. Mean As concentration in drinking water in towns ranged from 14 to 300 μg/l. Significant increased rate of serum alkaline phosphatase and total bilirubin was noted in subjects from the town with highest exposure in contrast to the town with lowest exposure (Hernandez-Zavala et al. 1998; NRC 2001). A study conducted by Santra et al. (1999) reported that bilirubin or alkaline phosphatase increases were not a characteristic finding in 93 patients with firm hepatomegaly attributed to chronic arsenicosis in West Bengal, India. A clinical diagnosis of chronic As poisoning from 69 patients revealed portal fibrosis in 63 (91.3%) cases, cirrhosis in 2 (2.9%) cases, and normal histology in 4 (5.8%) cases.

Renal system

In human, the kidneys are the major route of As excretion and seem to be less sensitive to As than most other organ systems (Mandal and Suzuki 2002). Target sites for As damage in the kidney include capillaries, tubules, and glomeruli (Mandal and Suzuki 2002). Recently Wang et al. (2008) studied a population in Xinjiang, China and reported As exposure is associated with kidney dysfunction.

Dermatological symptoms

Chronic exposure to As causes dermal effects such as melanosis, leucomelanosis, keratosis, Bowen's disease, and cancer (NRC 2001). Guo et al. (2001) investigated a dose–response relationship between As in drinking water and occurrence of arsenical dermatosis in two regions (Wuyuan and Alashan) of Inner Mongolia. In Wuyuan and Alashan, 96.2% and 69.3% of the tubewell water contained As exceeding 50 μg/l. Arsenical dermatosis prevalence was observed to be 44.8% in Wuyuan and 37.1% in Alashan of the 1,176 and 433 subjects studied, respectively. The study reported that the occurrence of arsenical dermatosis was predominant in people over 40 years of age. It was reported that chronic ingestion of As of $\geq$10 μg/kg per day may cause dermatosis and other types of As poisoning (USEPA 1992). A World Health Organization (WHO) (2001) report states that As exposure via drinking water is related to cancer in the lungs, kidney, bladder, and skin. Drinking water As concentrations of $\leq$50 μg/l have been associated with increased risks of cancer in the bladder and lung (WHO 2001).

Numerous investigators report the possible link between As exposure via drinking water and the occurrence of skin lesions from As-impacted areas of Bangladesh and West Bengal in India (Ahsan et al. 2000; Chakraborty and Saha 1987; Tondel et al. 1999; Guha Mazumder et al. 1998; Rahman et al. 2001; Chakraborti et al. 2002; Chowdhury et al. 2000). Tondel et al. (1999) investigated the association between prevalence of skin lesions and exposure to As in drinking water in four As-contaminated villages of Bangladesh. A total of 1,481 subjects were examined, and 430 had arsenical skin lesions. The concentration of As in drinking

Table 1 Relationship between As exposure and prevalence of arsenical skin lesions

Country, region	Health effect studied	Lowest concentration of As (μg/l)	References
Cordoba, Argentina	Recognizable signs of As toxicity	>100	Astolfi et al. (1981)
West Bengal, India	Arsenic dermatosis	200	Chakraborty and Saha (1987)
Niigata, Japan	Skin signs	>100	Tsuda et al. (1995)
West Bengal, India	Skin lesions (keratosis and hyperpigmentation)	<50	Guha Mazumder et al. (1998)
Bangladesh	Skin lesions (keratosis and melanosis)	≤150	Tondel et al. (1999)
Bangladesh	Skin lesions (keratosis and melanosis)	<50	Ahsan et al. (2000)
Inner Mongolia	Skin lesions (keratoses and hyperpigmentation)	<100	Tucker et al. (2001)
China	Skin lesions	>50	Guo et al. (2001)
West Bengal, India	Skin lesions	≥300	Chakraborti et al. (2004)
Inner Mongolia	Keratosis and pigment disorder	<50	Guo et al. (2006)

water ranged from undetectable to 2,040 μg/l. When the data was adjusted for age, the rate of skin lesions was found to increase from 18.6% and 17.9% in the lowest exposure group (≤150 μg/l of As) to 37.0% and 24.9% in the greatest exposure group (>1,000 μg/l of As) in males and females, respectively.

Chakraborty and Saha (1987) reported that the lowest As concentration in drinking water that produced As dermatosis was 200 μg/l, based on their study in 14 villages of West Bengal. Guha Mazumder et al. (1998) investigated the relationship between As-associated skin lesions of keratosis and hyperpigmentation in 7,683 subjects exposed to As via drinking water from As-affected areas of West Bengal. Age-adjusted prevalence of keratosis and hyperpigmentation increased from 0 and 0.3, respectively, in the lowest exposure category (<50 μg/l), to 8.3 and 11.5, respectively, per 100 in the highest exposure category (≥800 μg/l) for females. Age-adjusted keratosis and hyperpigmentation prevalence increased from 0.2 and 0.4, respectively, in the lowest exposure category (<50 μg/l), to 10.7 and 22.7, respectively, per 100 for males drinking water containing ≥800 μg/l of As.

A series of As dermatological skin lesions in arsenicosis patients of West Bengal, India, and Bangladesh have been reported (Rahman et al. 2001; Chakraborti et al. 2002; Chowdhury et al. 2000). The researchers have screened more than 100,000 villagers and registered 12,195 patients (about 12.2%) with arsenical skin lesions including melanosis, keratosis, hyperkeratosis, leucomelanosis, dorsal keratosis, skin cancer, etc. (Chakraborti et al. 2004). The researchers concluded that exposure to ≥300 μg As/l in drinking water for up to 2 years may cause arsenical skin lesions (Chakraborti et al. 2004). The lowest concentration of As in drinking water causing skin lesions was found to be <50 μg/l in a study conducted in West Bengal (Guha Mazumder et al. 1998). In a recent study from Inner Mongolia, Guo et al. (2006) reported 35 subjects with keratosis and 5 subjects with pigment disorder who drank water containing <50 μg/l of As. Of major concern is the finding reported from a Bangladesh study where relatively high rate of skin lesions was observed in people currently exposed to As level of <50 μg/l (Ahsan et al. 2000). Further epidemiological studies are needed to focus on adverse health effects on people who have been exposed to low levels of As. Arsenic exposure and prevalence of skin lesions are summarized in Table 1.

Neurological involvements

The occurrence of peripheral neuropathy is inconsistent in individuals chronically exposed to As in drinking water ranging from 100 to 1,000 μg/l (NRC 1999). Basu et al. (1996) reported sensory predominant distal polyneuropathy in eight patients with arsenical dermatoses in West Bengal, India, where As concentrations of the exposed subjects were 200–2,000 μg/l.

Neurological involvements due to As toxicity in the population exposed to As present in drinking water in

the four Indian states of West Bengal, Bihar, Uttar Pradesh, and Madhya Pradesh were reported in several publications (Chowdhury et al. 2000; Rahman et al. 2001; Mukherjee et al. 2003, 2005; Chakraborti et al. 1999, 2003; Ahamed et al. 2006a). These researchers concluded that exposure from As-contaminated groundwater in West Bengal and other states of India may produce neurological complications. Peripheral neuropathy is the predominant and common neurological complication of As toxicity (Mukherjee et al. 2003). Arsenic-induced toxic neuropathy is usually chronic and occasionally subacute in onset in these exposed studied populations (Mukherjee et al. 2003).

Recently Ahamed et al. (2006b) reported the neurological involvements in arsenicosis patients due to chronic As toxicity in a severely As-affected village of Bangladesh. The concentration of As in drinking water ranged from 300 to 1,584 μg/l. Tsai et al. (2003) conducted a cross-sectional study in Taiwan, reporting that long-term accumulated As may cause neurobehavioral effects in adolescence. Arsenic was found to range from undetectable levels to 3,590 μg/l. Wasserman et al. (2004) have shown that children's intellectual function can be decreased by increased As exposure. This correlation was proportional to dose, which means that children who had more than 50 μg/l As exposure had lower performance scores than children with less than 5.5 μg/l exposure. Recently Guo et al. (2007) reported appreciably higher neurotoxicity manifestations such as a decline in hearing, ability to taste, impacted vision, tingling, and numbness in As-affected villagers of Inner Mongolia.

Pregnancy outcomes

Aschengrau et al. (1989) reported an association between As exposure and occurrence of spontaneous abortions in eastern Massachusetts. The study showed that females who consumed As in water ranging from 1.4 to 1.9 μg/l had 1.7 times higher frequency of spontaneous abortion. Exposure to drinking water containing As in excess of 100 μg/l has been reported to lead to an excess of unprompted abortion, still birth, and perinatal mortality in Karcag in Hungary (Rudnai and Gulyas 1998). A similar effect of As exceeding 240 μg/l in water was found in a group of Bangladeshi women (Ahmad et al. 2001). Women exposed to As were found to show significant levels of As in umbilical cord and placenta; for example, Concha et al. (1998) reported the presence of As in the cord blood and placenta in women exposed to 200 μg/l of arsenic in their study in Argentina. In a study from northern Chile, high perinatal and neonatal mortality, and reduction in birth weight were reported with drinking water contaminated in the range 90–860 μg/l (Hopenhayn-Rich et al. 2000, 2003). Yang et al. (2003) reported a slightly high rate of preterm birth in an exposed population of Taiwan. The As concentration in drinking water ranged from undetectable to 3,590 μg/l.

A study reported the effects of As on reproductive health outcomes from Bangladesh (Kwok et al. 2006). A small but statistically significant association was reported between exposure to As and birth defects. However, there was no relationship between As exposure and stillbirth, low birth weight, childhood stunting, and child underweight in an investigation involving 2,006 pregnant women who were exposed to As in drinking water ranging from undetectable to 668 μg/l. Milton et al. (2005) reported that chronic exposure to high concentrations of As in drinking water posed excess risks for spontaneous abortion and stillbirth among the participants ($n = 533$) in their study. The concentration of As in drinking water in their study ranged from undetectable to 1,710 μg/l. Ahamed et al. (2006b) reported spontaneous abortions, stillbirths, and preterm births in women from a severely As-affected village, Eruani of Bangladesh. The range of As in the exposed group was 201–1,200 μg/l. Recently Rahman et al. (2007) reported that there was a significant dose response between As exposure and risk of infant death. The mean As concentration in drinking water was 239 μg/l.

A series of adverse obstetric outcomes have been documented in women subjected to As present in drinking water from the As-endemic areas of West Bengal, Bihar, and Uttar Pradesh states of India (Rahman et al. 2005; Mukherjee et al. 2005; Chakraborti et al. 2003; Ahamed et al. 2006a). An increased rate of spontaneous abortions, stillbirths, preterm births, low birth weights, and neonatal deaths was observed in women exposed to high level of As compared with women from noncontaminated areas. Recently Von Ehrenstein et al. (2006) studied obstetric outcomes and the rate of infant mortality among 202 women in West Bengal of India who were exposed to As exceeding 200 μg/l in drinking water.

They found that exposure to high concentrations of As during pregnancy increases the risk of stillbirth. No relationship was found between As exposure and spontaneous abortion and infant mortality.

Immunological system

The immune system response in human due to As toxicity has not been extensively investigated. In a study, Sakurai et al. (1998) reported that inorganic As is strongly toxic to macrophages and, at a concentration of 5 or 500 μM, the number of surviving cells decreased to 50%. A significant reduction in the phytohaemagglutinin (PHA)-induced proliferative response of lymphocytes from individuals exposed to 390 μg/l of As present in drinking water has been reported (Ostrosky-Wegman et al. 1991). Recently Islam et al. (2007) investigated the effect of exposure to As via drinking water with a mean As concentration of 216 μg/l and humoral immune response by measuring serum immunoglobulin profiles in As-affected subjects ($n = 125$) living in the As-endemic villages of Bangladesh. Mean duration of exposure in the patients was 7.4 years.

Diabetes mellitus

Diabetes mellitus has been linked to elevation of As in drinking water (Mandal and Suzuki 2002; Rahman et al. 1998, 1999a, b). This is consistent with numerous studies reporting the incidence of diabetes mellitus amongst people from the blackfoot-disease-endemic areas of Taiwan (Chen et al. 2007; Lai et al. 1994; Tsai et al. 1999). Tsai et al. (1999) reported mortality from diabetes mellitus among the residents exposed to As through drinking water (range 250–1,140 μg/l, median 780 μg/l) in blackfoot-disease-endemic areas of Southern Taiwan. In a cohort study conducted from As-endemic areas of Taiwan, Tseng et al. (2000) reported an incidence of diabetes mellitus in residents exposed to As in well water with As concentration ranging from 700 to 930 μg/l. Contrary to these observations, a study conducted in Millad County, UT, showed no significant increase in mortality from diabetes mellitus among subjects exposed to high concentration of As in drinking water (Lewis et al. 1999; Chen et al. 2007).

Recently Coronado Gonzalez et al. (2007) evaluated the effect of exposure to high levels of inorganic As in drinking water (20–400 μg/l) and the occurrence of type 2 diabetes mellitus in a population of an As-endemic region from Coahuila, a northern state of Mexico. They reported a dose–response relationship between As concentrations in urine and occurrence of type 2 diabetes mellitus.

Carcinogenic/cancer effects

Inorganic As is classified as a known human carcinogen (IARC 2004). This classification is based on strong epidemiological studies in humans. Table 2 shows the relationship of As exposure and some internal cancers. Based on previous US-EPA standard of 50 μg/l, Smith et al. (1992) estimated that the lifetime risk of dying from cancer from daily ingestion of 1 liter of water containing 50 μg/l As could be as high as 13 per 1,000 people exposed. The risk for the combined cancer mortality to be as high as 1 in 100 for people exposed to As level of 50 μg/l (Smith et al. 2002; NRC 1999, 2001). Astolfi et al. (1981) conducted a study in Cordoba, Northern Argentina, where they observed that regular intake of drinking water with As above 100 μg/l causes identifiable types of As toxicity and eventually in some cases leads to skin cancer. Excess mortality due to cancer among a cohort study involving 113 people exposed to As above 1000 μg/l was reported by Tsuda et al. (1995). The researchers reported standardized mortality ratios of 15.69 for lung cancer and 31.18 for urinary tract cancer (Tsuda et al. 1995). They also found similar risks for liver and uterine cancer. Wu et al. (1989) investigated the mortality rates of skin, lung, bladder, and kidney cancers in southwestern Taiwan. They obtained the highest elevation of odds ratio in skin cancer as 5.31 in males and 12.01 in females in the group exposed to As above 600 μg/l in drinking water compared with the group exposed to undetectable to 290 μg/l arsenic. Increased mortality was observed by Chen et al. (1985) in males and females in Taiwan due to lung, bladder, liver, and kidney cancers.

Hopenhayn-Rich et al. (1998) found a dose–response relationship between As in drinking water and increased risk of kidney and lung cancers in Argentina. The standardized mortality ratios from

Table 2 Relationship between arsenic exposure and internal cancers (NRC 2001)

Region	Parameter for arsenic exposure	Exposure levels	Cancer site	Outcome	References
Utah, USA	Cumulative lifetime exposure	19 to <33 mg	Bladder	Odds ratios: 1.56	Bates et al. (1995)
		33 to <53 mg		0.95	
		>53 mg		1.41	
Finland	Arsenic in drinking water	<0.1 μg/l	Bladder	Risk ratios: 1	Kurttio et al. (1999)
		0.1–0.5 μg/l		1.53	
		≥0.5 μg/l		2.44	
Chile	Arsenic in public water supply	0–10 μg/l	Lung	Odds ratios: 1	Ferreccio et al. (2000)
		10–29 μg/l		1.6	
		30–49 μg/l		3.9	
		50–199 μg/l		5.2	
		200–400 μg/l		8.9	
Nigata, Japan	Arsenic in drinking water	<0.05 μg/l	Lung	SMR: 0	Tsuda et al. (1995)
		0.05–0.99 μg/l		2.3	
		≥1.0 μg/l		15.7	
		<0.05 μg/l	Bladder	0	
		0.05–0.99 μg/l		0	
		≥1.0 μg/l		31.2	
Chile	Arsenic in drinking water	420 μg/l, mean	Bladder	SMR: 6.0 (male), 8.2 (female)	Smith et al. (1998)
			Lung	SMR: 3.8 (male), 3.1 (female)	
Cordoba, Argentina	Arsenic in drinking water	Low: <40 μg/l	Bladder	SMR: 0.80 (male)/1.21 (female)	Hopenhayn-Rich et al. (1998)
		Medium: 40–178 μg/l		1.42 (male)/1.58 (female)	
		High: >178 μg/l		2.14 (male)/1.82 (female)	
		Low: <40 μg/l	Kidney	SMR: 0.87 (male)/1.00 (female)	
		Medium: 40–178 μg/l		1.33 (male)/1.36 (female)	
		High: >178 μg/l		1.57 (male)/1.81 (female)	
		Low: <40 μg/l	Lung	SMR: 0.92 (male)/1.24 (female)	
		Medium: 40–178 μg/l		1.54 (male)/1.34 (female)	
		High: >178 μg/l		1.77 (male)/2.16 (female)	

Table 2 continued

Region	Parameter for arsenic exposure	Exposure levels	Cancer site	Outcome	References
Taiwan	Arsenic in drinking water	<300 μg/l	Bladder	MR: 22.6 (male)/25.6 (female)	Wu et al. (1989)
		300–590 μg/l		61.0 (male)/57.0 (female)	
		≥600 μg/l		92.7 (male)/111.3 (female)	
		<300 μg/l	Kidney	MR: 8.42 (male)/3.42 (female)	
		300–590 μg/l		18.90 (male)/19.42 (female)	
		≥600 μg/l		25.26 (male)/57.98 (female)	
		<300 μg/l	Lung	MR: 49.16 (male)/36.71 (female)	
		300–590 μg/l		100.67 (male)/60.82 (female)	
		≥600 μg/l		104.08 (male)/122.16 (female)	
		<10 μg/l	Urinary tract	RR: 1	Chiou et al. (2001)
		10–50 μg/l		1.5	
		50.1–100		2.2	
		>100 μg/l		4.8	

SMR Standard mortality rate, *MR* mortality rate, *RR* relative risk

low- to high-exposure groups (40–178 μg/l) were observed as 0.87–1.57 for males and 1.00–1.81 for females for kidney cancer, and 0.92–1.77 for male and 1.24–2.16 for female for lung cancer. Kurttio et al. (1999) investigated the effect of exposure to As (<0.05–64 μg/l, median 0.14 μg/l) present in drinking water and the incidence of bladder and kidney cancers in Finland. Statistically significant risk of bladder cancer was observed among people exposed to ≥0.5 μg/l As. No relationship was found between kidney cancer and As exposure.

Conclusion

Ingestion of inorganic As is an established cause of various skin lesions and subsequent skin cancer and other internal cancers such as lung, bladder, liver, and kidney cancers. Ingestion of As can also result in nonspecific gastrointestinal complaints such as diarrhea and cramping, and hematological effects including anemia and leucopenia. Adverse impacts on the neurological and reproductive systems are also noted in the population of As-affected areas. Numerous studies have also reported the possible effect of As exposure via drinking water on cardiovascular diseases as well as diabetes mellitus. More studies are required to focus on low levels of As exposure and its related health effects.

References

Ahamed, S., Sengupta, M. K., Mukherjee, A., et al. (2006a). Arsenic groundwater contamination and its health effects in the state of Uttar Pradesh (UP) in upper and middle Ganga plain, India: A severe danger. *Science of the Total Environment, 370*, 310–322.

Ahamed, S., Sengupta, M. K., Mukherjee, S. C., et al. (2006b). An eight year study report on arsenic contamination in groundwater and health effects in Eruani village, Bangladesh and an approach for its mitigation. *Journal of health, population and Nutrition, 24*, 129–141.

Ahmad, S. A., Sayed, M. H. S. U., Barua, S., et al. (2001). Arsenic in drinking water and pregnancy outcomes. *Environmental Health Perspectives, 109*, 629–631.

Ahsan, H., Perrin, M., Rahman, A., et al. (2000). Associations between drinking water and urinary arsenic levels and skin lesions in Bangladesh. *Journal of Occupational and Environmental Medicine, 42*, 1195–1201.

Aschengrau, A., Zeiler, S., & Cohen, A. (1989). Quality of community drinking water and the occurrence of

spontaneous abortion. *Archives of Environmental Health, 44*, 283–289.

Astolfi, E., Maccagno, A., Fernandez, J. C. G., et al. (1981). Relation between arsenic in drinking water and skin cancer. *Biological Trace Element Research, 3*, 133–143.

Basu, D., Dasgupta, J., Mukherjee, A., et al. (1996). Chronic neuropathy due to arsenic intoxication from geo-chemical source—a five year follow up. *JANEI, 1*, 45–47.

Bates, M. N., Smith, A. H., & Cantor, K. P. (1995). Case control study of bladder cancer and arsenic in drinking water. *American Journal of Epidemiology, 141*, 523–530.

Borgono, J. M., Vicent, P., Venturino, H., et al. (1977). Arsenic in the drinking water of the city of Antofagasta: Epidemiological and clinical study before and after the installation of a treatment plant. *Environmental Health Perspectives, 19*, 103–105.

Chakraborti, D., Biswas, B. K., Roy Chowdhury, T., et al. (1999). Arsenic groundwater contamination and sufferings of people in Rajnandangao, Madhya Pradesh, India. *Current Science, 77*, 502–504.

Chakraborti, D., Mukherjee, S. C., Pati, S., et al. (2003). Arsenic groundwater contamination in middle Ganga plain, Bihar, India: A future danger. *Environmental Health Perspectives, 111*, 1194–1201.

Chakraborti, D., Rahman, M. M., Paul, K., et al. (2002). Arsenic calamity in the Indian subcontinent—what lessons have been learned? *Talanta, 58*, 3–22.

Chakraborti, D., Sengupta, M. K., Rahman, M. M., et al. (2004). Groundwater arsenic contamination and its health effects in the Ganga–Meghna–Brahmaputra plain. *Journal of Environmental Monitoring, 6*, 74–83.

Chakraborty, A. K., & Saha, K. C. (1987). Arsenical dermatosis from tubewell water in West Bengal. *Indian Journal of Medical Research, 85*, 326–334.

Chen, C. J., Chuang, Y. C., Lin, T. H., et al. (1985). Malignant neoplasms among residents of a blackfoot disease endemic area in Taiwan: High arsenic artesian well water and cancers. *Cancer Research, 45*, 5895–5899.

Chen, C. J., Hsueh, Y. M., Lai, M. S., et al. (1995). Increased prevalence of hypertension and long term arsenic exposure. *Hypertension, 25*, 53–60.

Chen, C. J., Wang, S. L., Chiou, J. M., et al. (2007). Arsenic and diabetes and hypertension in human populations: A review. *Toxicology and Applied Pharmacology, 222*, 298–304.

Chiou, H. Y., Chiou, S. T., Hsu, Y. H., et al. (2001). Incidence of transitional cell carcinoma and arsenic in drinking water: A follow up study of 8102 residents in an arseniasis-endemic area in Northern Taiwan. *American Journal of Epidemiology, 153*, 411–418.

Chiou, H. Y., Huang, W. I., Su, C. L., et al. (1997). Dose response relation between prevalence of cerebrovascular diseases and ingested inorganic arsenic. *Stroke, 28*, 1717-1723.

Chowdhury, U. K., Biswas, B. K., Roychowdhury, T., et al. (2000). Groundwater arsenic contamination in Bangladesh and West Bengal, India. *Environmental Health Perspectives, 108*, 393–396.

Concha, G., Vogler, G., Lezcano, D., et al. (1998). Exposure to inorganic arsenic metabolites during early human development. *Toxicological Sciences, 44*, 185–190.

Coronado Gonzalez, J. A., Del Razo, L. M., Garcia-Vargas, G., et al. (2007). Inorganic arsenic exposure and type 2 diabetes mellitus in Mexico. *Environmental Research, 104*, 383–389.

Engel, R. R., & Smith, A. H. (1994). Arsenic in drinking water and mortality from vascular disease: An ecological analysis in 30 counties in the United States. *Archives of Environmental Health, 49*, 418–427.

Ferreccio, C., Gonzalez, C., Solari, J., et al. (2000). Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology, 11*, 673–679.

Guha Mazumder, D. N., Chakraborty, A. K., Ghosh, A., et al. (1988). Chronic arsenic toxicity from drinking tubewell water in rural West Bengal. *Bulletin of the World Health Organization, 66*, 499–506.

Guha Mazumder, D. N., Das Gupta, J., & Santra, A. (1997). Arsenic exposure and health effects. In C. O. Abernathy, R. L. Calderon, W. R. Chappell, et al. (Eds.), *Non-cancer effects of chronic arsenicosis with special reference to liver damage* (pp. 112–123). London: Chapman and Hall.

Guha Mazumder, D. N., Haque, R., Ghosh, N., et al. (1998). Arsenic levels in drinking water and the prevalence of skin lesions in West Bengal, India. *International Journal of Epidemiology, 27*, 871–877.

Guha Mazumder, D. N., Haque, R., Ghosh, N., et al. (2000). Arsenic in drinking water and the prevalence of respiratory effects in West Bengal, India. *International Journal of Epidemiology, 29*, 1047–1052.

Guo, X., Fujino, Y., Kaneko, S., et al. (2001). Arsenic contamination of groundwater and prevalence of arsenical dermatosis in the Hetao plain area, Inner Mongolia, China. *Molecular and Cellular Biochemistry, 222*, 137–140.

Guo, J. X., Hu, L., Yand, P. Z., et al. (2007). Chronic arsenic poisoning in drinking water in Inner Mongolia and its associated health effects. *Journal of Environmental Science and Health, 42*, 1853–1858.

Guo, X., Liu, Z., Huang, C., et al. (2006). Levels of arsenic in drinking water and cutaneous lesions in Inner Mongolia. *Journal of health, population and Nutrition, 24*, 214–220.

Harrington, J. M., Middaugh, J. P., Morse, D. L., et al. (1978). A survey of a population exposed to high concentrations of arsenic in well water in Fairbanks, Alaska. *American Journal of Epidemiology, 108*, 377–385.

Hernandez-Zavala, A., Del Razo, L. M., Aguiler, C., et al. (1998). Alteration in bilirubin excretion in individuals chronically exposed to arsenic in Mexico. *Toxicology Letters, 99*, 79–84.

Hernandez-Zavala, A., Del Razo, L. M., Garcia-Vargas, G. G., et al. (1999). Alter activity of heme biosynthesis pathways enzymes in individuals chronically exposed to arsenic in Mexico. *Archives of Toxicology, 73*, 90–95.

Hopenhayn Rich, C., Browning, S. R., Hertz-Picciotto, I., et al. (2000). Chronic arsenic exposure and risk of infant mortality in two areas of Chile. *Environmental Health Perspectives, 108*, 667–673.

Hopenhayn-Rich, C., Biggs, M. L., & Smith, A. (1998). Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. *International Journal of Epidemiology, 27*, 561–569.

Hopenhayn Rich, C., Ferreccio, C., Browning, S. R., et al. (2003). Arsenic exposure from drinking water and birth weight. *Epidemiology, 14*, 593–602.

IARC (International Agency for Research on Cancer). (2004). *IARC monograph 84: Some drinking water disinfectants and contaminants including arsenic*. Lyon: World Health Organization, International Agency for Research on Cancer (IARC).

Islam, L. N., Nabi, A. H. M. N., Rahman, M. M., et al. (2007). Association of respiratory complications and elevated serum immunoglobulins with drinking water arsenic toxicity in human. *Journal of Environmental Science and Health, 42*, 1807–1814.

Kapaj, S., Peterson, H., Liber, K., et al. (2006). Human health effects from chronic arsenic poisoning—a review. *Journal of Environmental Science and Health, 41*, 2399–2428.

Kurttio, P., Pukkala, E., Kahelin, H., et al. (1999). Arsenic concentrations in well water and risk of bladder and kidney cancer in Finland. *Environmental Health Perspectives, 107*, 705–710.

Kwok, R. K., Kaufmann, R. B., & Jakariya, M. (2006). Arsenic in drinking water and reproductive health outcomes: A study of participants in the Bangladesh integrated nutrition programme. *Journal of Health, Population and Nutrition, 24*, 190–205.

Lai, M. S., Hsueh, Y. M., Chen, C. J., et al. (1994). Ingested inorganic arsenic and prevalence of diabetes mellitus. *American Journal of Epidemiology, 139*, 484–492.

Lewis, D. R., Southwick, J. W., Ouellet-Hellstrom, R., et al. (1999). Drinking water arsenic in Utah: A cohort mortality study. *Environmental Health Perspectives, 107*, 359–365.

Mandal, B. K., & Suzuki, K. T. (2002). Arsenic round the world: A review. *Talanta, 58*, 201–235.

Michigan Department of Public Health. (1982). Arsenic in drinking water-A study of exposure and a clinical survey. Division of Environmental Epidemiology, Bureau of Disease Control and Laboratory Services. Environmental Health Statistics Unit, Technical Services Section, Office of Vital and Health Statistics, Department of Public Health, Lansing, Michigan.

Milton, A. H., Hasan, Z., Rahman, A., et al. (2001). Chronic arsenic poisoning and respiratory effects in Bangladesh. *Journal of Occupational Health, 43*, 136–140.

Milton, A. H., Hasan, Z., Rahman, A., et al. (2003). Non-cancer effects of chronic arsenicosis in Bangladesh: Preliminary results. *Journal of Environmental Science and Health, 38*, 301–305.

Milton, A. H., & Rahman, M. (2002). Respiratory effects and arsenic contaminated well water in Bangladesh. *International Journal of Environmental Health Research, 12*, 175–179.

Milton, A. H., Smith, W., Rahman, B., et al. (2005). Chronic arsenic exposure and adverse pregnancy outcomes in Bangladesh. *Epidemiology, 16*, 82–86.

Morton, W. E., & Dunnette, D. A. (1994). Health effects of environmental arsenic. In J. O. Nriagu (Ed.), *Arsenic in the environment. Part II: Human health and ecosystem effects* (pp. 17–34). New York: Wiley.

Mukherjee, S. C., Rahman, M. M., Chowdhury, U. K., et al. (2003). Neuropathy in arsenic toxicity from groundwater arsenic contamination in West Bengal-India. *Journal of Environmental Science and Health, 38*, 165–183.

Mukherjee, S. C., Saha, K. C., Pati, S., et al. (2005). Murshidabad—one of the nine arsenic-affected districts of West Bengal, India. Part II: Dermatological, neurological, and obstetric findings. *Journal of Toxicology: Clinical Toxicology, 43*, 835–848.

Naqvi, S. M., Vaishnavi, C., & Singh, H. (1994). Toxicity and metabolism of arsenic in vertebrates. In J. O. Nriagu (Ed.), *Arsenic in the environment. Part II: Human health and ecosystem effects* (pp. 55–92). New York: Wiley.

National Research Council (NRC). (1999). *Arsenic in drinking water*. Washington, DC: National Academy Press.

National Research Council (NRC). (2001). *Arsenic in drinking water—2001 update*. Washington, DC: National Academy Press.

Ng, J. C., Wang, J., & Shraim, A. (2003). A global health problem caused by arsenic from natural sources. *Chemosphere, 52*, 1353–1359.

Ostrosky-Wegman, P., Gonsebatt, M. E., Montero, R., et al. (1991). Lymphocyte proliferation kinetics and genotoxic findings in a pilot study on individuals chronically exposed to arsenic in Mexico. *Mutation Research, 250*, 477–482.

Rahman, M. M., Chowdhury, U. K., Mukherjee, S. C., et al. (2001). Chronic arsenic toxicity in Bangladesh and West Bengal, India—a review and commentary. *Clinical Toxicology, 39*, 683–700.

Rahman, M. M., Sengupta, M. K., Ahamed, S., et al. (2005). The magnitude of arsenic contamination in groundwater and its health effects to the inhabitants of the Jalangi—one of the 85 arsenic affected blocks in West Bengal, India. *Science of the Total Environment, 338*, 189–200.

Rahman, M., Tondel, M., Ahmad, S. A., et al. (1998). Diabetes mellitus associated with arsenic exposure in Bangladesh. *American Journal of Epidemiology, 148*, 198–203.

Rahman, M., Tondel, M., Ahmed, S. A., et al. (1999a). Hypertension and arsenic exposure in Bangladesh. *Hypertension, 33*, 74–78.

Rahman, M., Tondel, M., Chowdhury, I. A., et al. (1999b). Relations between exposure to arsenic, skin lesions and glucosuria. *Occupational and Environmental Medicine, 56*, 277–281.

Rahman, A., Vahter, M., Ekstrom, E. C., et al. (2007). Association of arsenic exposure during pregnancy with fetal loss and infant death: A cohort study from Bangladesh. *American Journal of Epidemiology, 165*, 1389–1396.

Rudnai, P., & Gulyas, E. (1998). Adverse effects of drinking water related arsenic exposure on some pregnancy outcomes in Karcag, Hungary, In: *Book of Abstracts, 3rd International Conference on Arsenic Exposure and Health Effects* (116 pp), July 12–15, San Diego, CA, 1998.

Sakurai, T., Kaise, Y., & Matsubara, C. (1998). Inorganic and methylated arsenic compounds induce death in murine macrophages via different mechanisms. *Chemical Research in Toxicology, 11*, 273–283.

Santra, A., Dasgupta, J., De, B. K., et al. (1999). Hepatic manifestations in chronic arsenic toxicity. *Indian Journal of Gastroenterology, 18*, 152–155.

Smith, A., Goycolea, M., Haque, R., et al. (1998). Marked increase in bladder and lung cancer mortality in a region

of Northern Chile due to arsenic in drinking water. *American Journal of Epidemiology, 147*, 660–669.

Smith, A. H., Hopemhayn-Rich, C., Bates, M. N., et al. (1992). Cancers risks from arsenic in drinking water. *Environmental Health Perspectives, 97*, 259–267.

Smith, A. H., Lopipero, P. A., Bates, M. N., et al. (2002). Arsenic epidemiology and drinking water standards. *Science, 296*, 2145–2146.

Terada, H., Sasaga, T., Saito, H., et al. (1962). Chronic arsenical poisoning and hematopoietic organs. *Acta Medica et Biologica, 9*, 279–292.

Tondel, M., Rahman, M., Magnuson, A., et al. (1999). The relationship of arsenic levels in drinking water and the prevalence rate of skin lesions in Bangladesh. *Environmental Health Perspectives, 107*, 727–729.

Tsai, S. Y., Chou, H. Y., The, H. W., et al. (2003). The effects of chronic arsenic exposure from drinking water on the neurobehavioral development in adolescence. *Neuro Toxicology, 24*, 747–753.

Tsai, S. M., Wang, T. N., & Ko, Y. C. (1999). Mortality for certain diseases in areas with high level of arsenic in drinking water. *Archives of Environmental Health, 54*, 186–193.

Tseng, C. H., Chong, C. K., Chen, C. J., et al. (1996). Dose–response relationship between peripheral vascular disease and ingested arsenic among residents in blackfoot disease endemic villages in Taiwan. *Atherosclerosis, 120*, 125–133.

Tseng, C. H., Tai, T. Y., Ching, C. P., et al. (2000). Long term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: A cohort study in arseniasis hyperendemic villages in Taiwan. *Environmental Health Perspectives, 108*, 847–851.

Tsuda, T., Babazono, A., Yamamoto, E., et al. (1995). Ingested arsenic and internal cancer: A historical cohort study followed for 33 years. *American Journal of Epidemiology, 141*, 198–209.

Tucker, S. B., Lamm, S. H., Li, F. X., et al. (2001). Relationship between consumption of arsenic contaminated well water and skin disorders in huhhot, Inner Mongolia. Inner Mongolia Cooperative Arsenic Project Study. Final Report. Department of Dermatology, University of Texas, Houston and Department of Environmental Epidemiology, Institute of Environmental Engineering, Chinese Academy of Preventive Medicine, Beijing, China, July 5.

USEPA (US Environmental Protection Agency). (1992). Draft drinking water criteria document on arsenic submitted by Human Risk Assessment Branch, Health and Ecological Criteria Division, Office of Science and Technology, Office of water, US Environmental Protection Agency, Washington, DC.

Von Ehrenstein, O. S., Guha Mazumder, D. N., Smith, M. H., et al. (2006). Pregnancy outcomes, infant mortality and arsenic in drinking water in West Bengal, India. *American Journal of Epidemiology, 163*, 662–669.

Wang, C. H., Hsiao, C. K., Chen, C. L., et al. (2007). A review of the epidemiologic literature on the role of environmental arsenic exposure and cardiovascular diseases. *Toxicology and Applied Pharmacology, 222*, 315–326.

Wang, J. P., Wang, S. L., Lin, Q., et al. (2008). Association of arsenic and kidney dysfunction in people with diabetes and validation of its effects in rats. *Environmental International*. doi:10.1016/j.envint.2008.07.015.

Wasserman, G. A., Liu, X., Parvez, F., et al. (2004). Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. *Environmental Health Perspectives, 112*, 1329–1333.

WHO (World Health Organization). (2001). *IPCS environmental health criteria 224 Arsenic and arsenic compounds*. Geneva: International Programme on Chemical Safety, World Health Organization.

Wu, M. M., Kuo, T. L., Hwang, Y. H., et al. (1989). Dose–response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *American Journal of Epidemiology, 130*, 1123–1132.

Yang, C. Y. (2006). Does arsenic exposure increase the risk of development of peripheral vascular diseases in humans? *Journal of Toxicology and Environmental Health, 69*, 1797–1804.

Yang, C. H., Chang, C. C., Tsai, S. S., et al. (2003). Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in northeastern Taiwan. *Environmental Research, 91*, 29–34.

Yoshida, T., Yamauchi, H., & Sun, G. F. (2004). Chronic health effects in people exposed to arsenic via the drinking water: Dose–response relationships in review. *Toxicology and Applied Pharmacology, 198*, 243–252.

Zierold, K. M., Knobeloch, L., & Anderson, L. (2004). Prevalence of chronic diseases in adults exposed to arsenic-contaminated drinking water. *American Journal of Public Health, 94*, 1936–1937.