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Human Health Effects From Chronic Arsenic Poisoning–A Review

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The ill effects of human exposure to arsenic (As) have recently been reevaluated by government agencies around the world. This has lead to a lowering of As guidelines in drinking water, with Canada decreasing the maximum allowable level from 50 to 25 μg/L and the U.S. from 50 to 10 μg/L. Canada is currently contemplating a further decrease to 5 μg/L. The reason for these regulatory changes is the realization that As can cause deleterious effects at lower concentrations than was previously thought. There is a strong relationship between chronic ingestion of As and deleterious human health effects and here we provide an overview of some of the major effects documented in the scientific literature. As regulatory levels of As have been decreased, an increasing number of water supplies will now require removal of As before the water can be used for human consumption. While As exposure can occur from food, air and water, all major chronic As poisonings have stemmed from water and this is usually the predominant exposure route. Exposure to As leads to an accumulation of As in tissues such as skin, hair and nails, resulting in various clinical symptoms such as hyperpigmentation and keratosis. There is also an increased risk of skin, internal organ, and lung cancers. Cardiovascular disease and neuropathy have also been linked to As consumption. Verbal IQ and long term memory can also be affected, and As can suppress hormone regulation and hormone mediated gene transcription. Increases in fetal loss and premature delivery, and decreased birth weights of infants, can occur even at low ($<$10 μg/L) exposure levels. Malnourished people have been shown to be more predisposed to As-related skin lesions. A large percentage of the population (30–40%) that is using As-contaminated drinking water can have elevated As levels in urine, hair and nails, while showing no noticeable clinical symptoms, such as skin lesions. It is therefore important to carry out clinical tests of As exposure.

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Factors combining to increase/decrease the ill effects of As include duration and magnitude of As exposure, source of As exposure, nutrition, age and general health status. Analytical determinations of As poisoning can be made by examining As levels in urine, hair and toenails. Communities and individuals relying on groundwater sources for drinking water need to measure As levels to ensure that their supplies are safe. Communities with water As levels greater than 5 μg/L should consider a program to document As levels in the population.

Key Words: Arsenic; Drinking water; Chronic toxicity; Cancer; Hyperpigmentation; Hair and toenail arsenic.

INTRODUCTION

Human health effects caused by exposure to arsenic (As) have been highlighted by recent regulatory initiatives in the U.S. This includes three panel reviews: The National Academy of Sciences, The National Drinking Water Advisory Council, and the U.S. Environmental Protection Agency's (EPA's) Science Advisory Board. This work led the US EPA to lower the maximum As contaminant level in drinking water to 10 μg/L. All public water systems in the U.S. must comply with the 10 μg/L standard beginning January 23, 2006. A brief review of the panels findings are highlighted below.[1,2]

Human health effects caused by As exposure were key in panel assessments that resulted in the lowered U.S. As guideline. Health effects were dependent on the duration and dose of exposure. The National Research Council (NRC, the operating arm of the National Academy of Sciences) confirmed that the chronic effects of inorganic As exposure via drinking water include skin lesions, such as hyperpigmentation, and respiratory symptoms, such as cough and bronchitis. The cardiovascular, gastrointestinal and urinary systems were some of the other systems most affected in humans. This review also concluded that there was sufficient evidence to link bladder and lung cancers with ingestion of inorganic As. In addition, ailments linked to As included increased risk of high blood pressure and diabetes. The NRC accepted the fact that there is a need for more data to confirm the link between the As ingestion and negative effects on reproductive outcomes. The NRC underlined that there are differences in outcomes due to factors contributing to risk, such as exposure in different population groups. Evidence adds to the fact that As exposure may cause adverse effects, but this evidence is not conclusive because studies lack information on lifestyle, and other exposures that could affect health outcomes. The NRC also concluded that infants and children may be at greater risk for both cancer and non-cancer effects because of greater consumption via drinking water on a body-weight basis.[3] The US EPA indicated that lowering of the As guideline from 50 to 10 μg/L could prevent deaths from bladder, lung and skin cancers, and from heart disease.[2]

Similarly, Canada is also reevaluating As contamination of drinking water. The proposed maximum acceptable concentration for As in drinking water is 5 μg/L. However, Health Canada has set the current guideline at 25 μg/L. This guideline has been put in place temporarily until improved treatment technologies have been developed to further reduce As levels in drinking water to 5 μg/L.[4] As is of greatest concern in groundwater supplies where it is a naturally occurring mineral. Reducing the current level of As in drinking water will have a significant impact on communities across Canada because groundwater is a major water source in many rural, small communities. The Word Health Organization (WHO) has also reviewed As guidelines in drinking water and established a provisional guideline of 10 μg/L after concluding that inorganic As is a human carcinogen and that the main route of exposure is through drinking water and food.[5]

The interest in As has also resulted in the publication of several recent books, including *Aquatic Arsenic Toxicity and Treatment*[6] and *Natural Arsenic in Groundwater: Occurrence, Remediation and Management*.[7] Several review articles have also been published, including Yoshida et al.,[8] Luster and Simeonova,[9] Watanabe,[10] Tchounwou et al.,[11] Rossman et al.,[12] Mahata et al.,[13] Kitchin,[14] and Ratnaike.[15] Throughout this review it is important to mention that, whenever not stated otherwise, "arsenic" means total inorganic As.

PATHWAYS OF ARSENIC EXPOSURE

Arsenic Exposure Through Drinking Water

Groundwater with elevated concentrations of As has been recognized as a problem of global concern.[16-18] As contamination of groundwater is one of the principal pathways of human exposure to inorganic As. Elevated concentrations of As have been reported from several regions of the world[19] (Table 1) resulting primarily from natural sources, such as erosion and leaching from geological formations, although sometimes from anthropogenic sources, such as uses of As for industrial purposes, mining activities and metal processing, and application of pesticides and fertilizers containing As. The risk of As contamination is generally much higher in groundwater compared to surface water.

Natural occurrence of As in groundwater (>10 μg/L) is reported from many parts of the United States, such as California, Alaska, Arizona, Indiana, Idaho, Nevada, Washington, Missouri, Ohio, Wisconsin, and New Hampshire.[20–25] Higher concentrations of As are also found close to areas of geothermal fields, uranium and gold mining.[26] Natural occurrences of As have also been found in Canada,[27] Argentina,[28–31] Mexico,[32–34] Chile,[35,36] Taiwan,[37,38]

Table 1: Comparison of arsenic occurrences in groundwater from selected parts of the world (Courtesy of Naidu and Bhattacharya).[19]

Country/Region	Area affected	Depth of well	Arsenic conc. (μg/L)	Mechanism of contamination
Bangladesh, BDP (52 districts)	118, 012 km^2	8–260 m	$<2\rightarrow900$	Reduction of Fe-oxyhydroxides/Sulfide oxidation(?) in alluvial sediments
West Bengal, India, BDP (8 districts)	34 000 km^2	14–132 m	<1–1300	Reduction of Fe-oxyhydroxides/Sulfide oxidation (?) in alluvial sediments
China, Xinjiang Inner Mongolia (HAB)	4800 km^2	Shallow/Deep	<50–1860	Reducing environment in alluvial sediments
Taiwan	—	Deep	Up to 1820	Oxidation of pyrite in mine tailings
Thailand (10 districts)	10 districts	Shallow	120–6700	Oxidation of mine wastes and tailings
Ghana	1600 km^2	70–100 m		Oxidation of arsenopyrite in mine tailings
Argentina (Chaco-Pampean Plains)	10 million km^2	Shallow aquifers	100–4800	Volcanic ash with 90% rhyolitic glass
Chile	—	Shallow and deep wells	100–1000	Volcanic ash
Mexico, Zimapan, Lagunera	—	Shallow and deep wells	300–1100	Oxidation of sulfide from mine wastes
Hungary (Great Hungarian Plain)	4263 km^2	80–560 m	$25\rightarrow50$	Complexation of arsenic with humic substances
USA	Large areas	53–56 m	$100\rightarrow500$	Desorption of arsenic from Fe-oxyhydroxides/Sulfide oxidation
Canada (Nova Scotia)	—	8–53 m	18–146	Oxidation of sulfides
United Kingdom (Cornwall)	—	Shallow wells	>10	Oxidation of sulfides from mine wastes

China,[39,40] Japan,[41] southern Thailand,[42] Ghana,[43] Hungary,[44] and Finland.[45] Occurrence of As in groundwater of the Bengal Delta Plain in West Bengal, India and Bangladesh, is the region's single largest emerging societal and environmental problem of the present century.[46–56] Similar As problems also exist in the Flood Plain aquifers of the Mekong Delta in Cambodia and the Red River Delta in Vietnam,[57] where drinking water supplies are primarily based on groundwater resources.[58-62] Here, a population of over 20 million has resorted to groundwater use to meet agricultural productivity and increased drinking water demand.[57,60]

Drinking Water Criteria for Arsenic

Arsenic in drinking water can affect human health and is considered as one of the most significant environmental causes of cancer in the world.[63] Therefore, it is necessary to document the levels of As in drinking water, and its chemical speciation, and for establishing regulatory standards and guidelines.[21] The FAO health limit for As in groundwater was until recently 50 μg/L, but in view of recent incidences of As poisoning in the Indian subcontinent, a decrease to 5–10 μg/L is being considered by a number of regulatory bodies throughout the world. The temporary WHO guideline for As in drinking water is 10 μg/L. This is based on a 6×10^{-4} excess skin cancer risk, which is 60 times higher than the factor normally used to protect human health. However, the WHO states that the health-based drinking water guideline for As should in reality be 0.17 μg/L. Previously, such low levels were not feasible to determine as many analytical techniques had detection limits of 10 μg/L, which is why the less protective guideline was adopted.[64–66]

The US EPA drinking water standard for As was set at 50 μg/L in 1975, based on a Public Health Service standard originally established in 1942.[67] On the basis of investigations initiated by the National Academy of Sciences, it was concluded that this standard did not eliminate the risks of skin, lung, and prostate cancer from long-term exposure to low As concentrations in drinking water. In addition, there are several non-cancer effects related to ingestion of As at low levels, which include cardiovascular disease, diabetes, and anemia, as well as reproductive, developmental, immunological, and neurological disorders. In order to achieve the EPA's goal of protecting public health, recommendations were made to lower the safe drinking water limit to 5 μg/L, slightly higher than what is considered the technically feasible measurable level (3 μg/L).[68] Recently, the US EPA has established a health-based, non-enforceable Maximum Contaminant Level Goal (MCLG) of zero As and an enforceable Maximum Contaminant Level (MCL) of 10 μg As/L in drinking water.[69] This would apply to both non-transient, non-community water systems, as well as to the community water systems, as opposed to the previous MCL of 50 μg As/L set by the US EPA in 1975. However, the current

drinking water guideline for As adopted by both the WHO and the US EPA is 10 μg/L. This is higher than the proposed Canadian and Australian maximum permissible concentrations of 5 and 7 μg As/L, respectively.

Arsenic Exposure Through Coal Combustion and Incineration of Preserved Wood Products

Combustion of high As bearing coals is known to be a principal pathway of As emission in Guizhou province of southwestern China.[70,71] Open coal-burning stoves used for drying chili peppers have been the principal cause for chronic As poisoning to a population of nearly 3,000. Fresh chili peppers have less than 1 mg/kg As, while the chili peppers dried over high-As coal fires were reported to contain more than 500 mg/kg As.[70] Consumption of other tainted foods, ingestion of kitchen dust containing as high as 3000 mg/kg As, and inhalation of indoor air polluted by As from coal combustion are the other causes of chronic As poisoning. A possible pathway for exposure through air-particulates is the incidental use of preserved wood in open fires, indoors or outdoors.

Incineration of preserved wood products, pressure treated with chromated copper arsenate was found to be a source of As contamination to the environment.[72] The content of As in air-particulates from open fires was found to exceed the German air quality standards by a 100-fold.[73] The ashes, spread on lawns and vegetable cultivations, pose further risk to human health. In addition, tobacco smoke is another source of As emission in indoor environment. It is interesting to note that mainstream cigarette smoke contains 0.04 to 0.12 μg As per cigarette.[74]

HEALTH EFFECTS OF ARSENIC EXPOSURE

Terminology

Arsenicosis is a chronic illness resulting from drinking water with high levels of As over a long period of time. It is commonly known as As poisoning. Arseniasis means chronic arsenical poisoning, also called arsenicalism; the term arsenicism refers to a disease condition caused by slow poisoning with As.

Despite the existence of recent reviews, there does not appear to be a concise overview of the human health issues caused by As. This review is an attempt to address that gap. In addition, we address analytical approaches that can be used to determine human As exposures even after the As has been removed from the drinking water. The review is aimed to help health workers, practicing rural physicians, water treatment plant operators, government agencies, and community groups dealing with issues of human As exposure

and effects. Together, we need to put the safeguards in place to avoid adverse human health effects from chronic As exposure.

Arsenic and Cancer

The International Agency for Research on Cancer (IARC) has listed As as a human carcinogen since 1980.[75] Many researchers have underlined the potential risk that As in drinking water plays in human health. The positive association between As exposure and cancer has been evaluated by many researchers in different countries including the USA, Taiwan, Bangladesh, India, Argentina, and Chile, to name a few. This section highlights work performed during the last 4 to 5 years.

In a recent publication, Centeno et al.[76] report that As is a unique carcinogen. It is the only known human carcinogen for which there is adequate evidence of carcinogenic risk by both inhalation and ingestion. In a very detailed study spanning a 7-year period, Rahman et al.[77] indicated that As-affected patients in West Bengal had severe skin lesions. It was not clear what number of patients suffered from cancers, because they were too poor to afford the investigations. However, patients that had premature death due to cancer had serious arsenical skin lesions prior to that. Also, in follow-up visits, people that were exposed to high levels of As from drinking water and/or food for many years were frequently developing cancer. These small communities in West Bengal use groundwater sources for drinking, and this study showed that intervention of water management is critical.

Taiwanese studies investigated the risk association at 50 μg/L As in drinking water, the standard that was being reevaluated by the US EPA at that time. Data from Taiwan indicated that there is increased risk of internal cancers from As exposure through drinking water.[78] In a follow-up study of 8102 residents from an arseniasis-endemic area in Northeastern Taiwan, the association between ingested As and risk of cancers of urinary organs was investigated. It indicated that residents being exposed to well water As for 40 years or more had greater chances of getting urinary tract cancer than residents that had less than 40 years of exposure.[79] Conclusions from these studies suggested that the US EPA needed to revise the 50 μg/L As standard, which has now been done.[3] It is believed that there is a long latent stage between the time that humans are exposed to As and final cancer diagnosis.[79–81] In addition, Ferrecio et al.[82] presented a positive correlation between ingestion of inorganic As and lung cancer in humans in Chile. It is already known that cigarette smoking is a main risk factor for lung cancer, but the authors found that cigarette smoking plus ingestion of As from drinking water had a synergistic effect.

Skin Cancer

A significant relationship between As exposure and skin cancer has been observed. In a review, Rossman et al.[12] pointed out that arsenite can play a role in the enhancement of UV-induced skin cancers. The mechanism of action may involve effects on DNA methylation and DNA repair. In addition, Luster and Simeonova[9] reported epidemiological evidence indicating that As is associated with cancers of skin and internal organs, as well as with vascular disease.

Bladder Cancer

In a major U.S. study conducted on a population with chronic As exposure through drinking water, Steinmaus et al.[80] did not find a clear association between bladder cancer risk and exposure. The risks were lower than those in Taiwan with high As exposure.[78] However, in the U.S. study there was an elevated risk of bladder cancer in smokers that were exposed to As in drinking water near 200 μg/L, compared with smokers consuming lower As levels. These data suggest that As is synergistic with smoking at relatively high As levels (200 μg/L). Steinmaus et al.[80] highlighted that latency of As exposure causing bladder cancer can be very long (more than 40 years).

Lung Cancer

Hopenhayn-Rich et al.[83] found that mortality from lung cancer was significantly increased with increasing As ingestion. In addition, As and cigarette smoke are synergistic, thus increasing the risk of lung cancer. In a recent Taiwanese study, residents in arseniasis-endemic areas were followed during an 8-year period.[84] An increased risk of lung cancer was associated with high levels of As exposure via drinking water. The authors suggested that reduction in As exposure should reduce the lung cancer risk in cigarette smokers. Southwest Taiwan has been a region that used wells with high As levels for the past 5 decades. Researchers looked at lung cancer mortality versus standard mortality ratio (SMR). Their study further indicated that the mortality from lung cancer declined after the levels of As in the well water were reduced.[85]

China is another country where millions of people are exposed to elevated levels of As. In the review of Xia and Liu,[86] it was stressed that chronic arsenism in China is a serious health issue, which the authorities are now trying to tackle. Measures are being implemented to improve drinking water sources, patient treatment, and health education. However, in As-endemic areas it is predicted that cancer incidence may increase over the next 10–20 years mainly due to previous exposures. This shows that urgent effective prevention is needed. Often in China, areas that have chronic arsenism also

have increased levels of fluoride in the drinking water. There are suggestions that the combination of the two could increase the risk to human health due to potential synergism. This should be further evaluated.

In a study with mice, Wu et al.[87] found that chronic low-level As exposure may affect heme metabolism, causing porphyrin changes. These changes may appear in the beginning stages of arsenicosis, before the carcinogenesis and can be a clinical indicator to diagnosis.

NON-CARCINOGENIC EFFECTS OF CHRONIC ARSENIC EXPOSURE

Neurobehavioral and Neuropathic Effects

In a cross-sectional study in Taiwan, Tsai et al.[88] suggested that long-term accumulated As may cause neurobehavioral effects in adolescence; therefore consumption of As in childhood may affect behavior later in life. In addition, these effects will be more severe if lead is present, because of synergistic effects. This facet of As toxicity needs to be addressed further.

Arsenic neuropathy is a recognized complication of As toxicity. Peripheral neuropathy (an abnormal and usually degenerative state of the peripheral nerves) due to chronic As exposure is one of the most common complications of the nervous system. The neuropathy is usually sensor (affects sensation), and the course of development is chronic. Patients can suffer from constant pain, hypersensitivity to stimuli, muscle weakness, or atrophy.[89,90] Sensory and sensorimotor (sensation and muscles are affected) neuropathy have also been observed.[77] The authors suggest that neurological symptoms are more frequently associated with people that have chronic As exposure, so duration, amount of As exposure, and nutritional factors together may affect As toxicity.

Effects on Memory and Intellectual Function

A study of children in Mexico found that urinary As concentration was inversely associated with verbal IQ and long-term memory. In addition, it was found that long-term memory, attention and the ability to understand speech may be affected by exposure to As in people with chronic malnutrition.[91] Wasserman et al.[92] have also shown that children's intellectual function can be decreased by increased As exposure. This correlation was proportional to the dose, which means children that had more than 50 μg/L As exposure had lower performance scores than children with less than 5.5 μg/L exposure. However, this study was limited to a certain period of time for a certain group of the population and some questions remained unanswered, like the role of exposure to As on the intellectual functions, and developing a better understanding of exposure-outcome by follow-up at an earlier age.

In addition, Watanabe et al.,[10] evaluating the effects of As at different ages, found that age is a very important factor when evaluating effects. In younger generations, clinical manifestations are not always obvious and, as a result, can be missed or underestimated, producing complications later. Effects of early-life exposure are not well understood compared with the effects of adult exposure.

Reproductive Effects

In a study by Chakraborti et al.,[93] pregnancy complications were found to be due to chronic exposure from groundwater As. They found a positive trend in women, with increased As exposure leading to increased fetal loss and premature delivery. Furthermore, research on the effects of As exposure in rats has shown that As causes necrosis (death of living tissue), apoptosis (programmed cell death), loss of conception in the uterus, and death of the newborn.[94] Toxic effects on the fetus were also suggested by Hopenhayn et al.,[95] who reported that women with chronic exposure to As (less than 50 μg/L) in drinking water were predisposed to decreased birth weight of infants, suggesting that As may reduce the development of the fetus in utero. Reproductive effects should be further studied to confirm the risks to humans.

A separate study by Hopenhayn et al.[96] found that women exposed to As in drinking water during pregnancy have changes in urinary excretion and metabolite distribution that can cause toxic effects on the developing fetus. As metabolism changes during pregnancy, so the impact on the fetus may be different at different stages of pregnancy. It is suggested that this may affect the health in premature and full-term babies. The effects of As exposure through drinking water on pregnancy outcomes were also assessed in a recent study by Milton et al.[97] This study indicated a strong link between chronic As exposure and spontaneous abortion and stillbirth. However, further studies are needed to confirm the association between As and negative pregnancy outcomes.

Steatosis (Fatty Liver)

Chen et al.[98] studied the effects of As in mouse liver and concluded that chronic oral inorganic As exposure caused cellular hypertrophy (enlargement of the cell) and steatosis. It was suggested that this may cause DNA methylation, which is thought to play a key role in the control of gene expression in mammalian cells, which is important in oncogenesis in mammals.

Cardiovascular Disease

Lee et al.[99] reported that As ingestion affects the platelets. Platelets are key players in cardiovascular disease. In the presence of thrombin, trivalent As (arsenite) was observed to increase platelet aggregation. In vivo, As in drinking water increased arterial thrombus formation in rats. The authors indicated that platelet aggregation increased with long-term exposure to As in drinking water, being one of the factors causing cardiovascular disease. The authors proposed that their results may be used for estimation of risks from thrombosis and cardiovascular disease in humans, but further evidence is necessary to support their findings.

Ischemic Heart Diseases (IHD)

Ischemia is localized tissue anemia due to obstruction of the inflow of arterial blood. In a study in arseniasis hyper-endemic villages in southwest Taiwan, researchers evaluated a possible relationship between long-term As exposure and IHD. This study included 462 individuals living in a blackfoot-disease (BFD) area that were drinking well-water for many years. The study indicated that 78 subjects (16.9%) had IHD. Looking at age groups, the highest rate of IHD was for individuals $\geq$60 years old (about 31%). This suggests that the prevalence of IHD increased with increasing duration of consuming artesian well-water.[100]

Carotid Atherosclerosis

The carotid arteries are a chief pair of arteries that pass up the neck and supply the head including the brain. Wang et al.[101] highlighted that long-term exposure to As is an independent risk factor for atherosclerosis. Long-term exposure to As is associated with increased risk of carotid atherosclerosis and they suggested that carotid atherosclerosis is an excellent biomarker for arseniasis.

Respiratory System Diseases

Based on separate studies in Bangladesh and West Bengal (India), it was concluded that, in addition to skin lesions, chronic exposure to As can cause respiratory system effects such as chronic cough and chronic bronchitis.[90,102] In another study, Milton et al.[103] underlined the fact that patients with chronic As exposure have skin manifestations associated with weakness, conjuctival congestion, redness of the eyes, chronic cough, and chronic bronchitis (inflammation of the respiratory tract). This work strengthens the evidence that long-term ingestion of As can cause adverse effects on the respiratory system.[102,103]

Effects on Hormonal System

Arsenic is thought to be an endocrine disruptor, able to alter hormone gene transcription at doses as low as 0.4 μg/L arsenite. Different doses of As can affect hormone regulation in cells at different levels. It is suggested that As effects on gene expression may depend on internal conditions in the human body. Different organs in the body will respond differently to As exposure.[104]

Diabetes Mellitus-Type Two Diabetes

Type-two diabetes mellitus is non-insulin dependent diabetes, which generally occurs after 40 years of age, with the highest risk in obese people and people that have a family history of diabetes. Tseng et al.[105,106] suggest that inorganic As is diabetogenic in humans, but little is known about pathophysiological mechanisms. They underline the fact that people exposed to As suffer from type two-diabetes. However, there are some limitations in the study design that weakens the evidence reported.

Other Effects

Guha Mazumder[90] confirms the findings of previous studies in that chronic exposure to As is associated with pigmentation, keratosis, skin cancer, weakness, anemia, dyspepsia, enlargement of the liver, spleen, and ascites (fluid in abdomen). Other symptoms included chest problems like cough, restrictive lung disease, polyneuropathy, altered nerve conduction velocity, and hearing loss. In West Bengal, India, people are endemically exposed to more than 50 μg/L As in drinking water. Patients reported having irritability, lack of concentration, depression, sleep disorders, headaches, fatigue, skin itching, burning of eyes, weight loss, anemia, chronic abdominal pain, diarrhea, edema of feet, liver enlargement, spleen enlargement, cough, joint pain, decreased hearing, decreased vision, loss of appetite, and weakness. Liver enzymes were increased and liver histology showed fibrosis (fibrotic tissue in liver). Other symptoms included cirrhosis (end stage of hepatic reaction to liver parencymal cell injury), hematemesis (vomiting with blood), and melena (the passage of dark, pitchy and grumous stools stained with blood pigments or with altered blood). It was found that the longer the time of exposure, the more severe the signs and symptoms of As toxicity.[89,90] Table 2 shows some of the most common toxic effects that can result from chronic As exposure.

Subclinical Effects

Clinical As symptoms depend on the duration of exposure, with signs and symptoms appearing at later stages and with diseases progressing in silent conditions at earlier stages. Rahman et al.'s[77] study in West Bengal

Table 2: Studies documenting toxic effects of chronic As exposure.

Study	Study type	Toxic effects	Country
Mukherjee et al.[84]	Cohort	Peripheral neuropathy	India
Milton et al.[92]	Cross-sectional	Fetal and infant death, spontaneous abortion	Bangladesh
Hopenhayn et al.[90]	Cohort	Reduction in birth weight	Chile
Steinmaus et al.[75]	Case-control	Bladder cancer	USA
Tseng et al.[100,101]	Cohort	Diabetes	Taiwan
Hopenhayn-Rich et al.[78]	Ecological	Lung, kidney cancers	Argentina
Smith et al.[103]	Cross-sectional	Skin lesions	Chile
Kurttio et al.[105]	Cohort	Bladder cancer	Finland
Lee et al.[94]	in vivo/in vitro rats	Platelet aggregation, thrombus formation	Korea
Milton and Rahman [97]	Case-control	Cough, bronchitis	Bangladesh
Morales et al.[73]	Case-control	Lung, bladder cancer	Taiwan
Rahman et al.[106]	Cross-sectional	Hypertension	Bangladesh
Rahman et al.[72]	Cohort	Skin cancer, gangrene, neuropathy	West Bengal (India)
Tsai et al.[83]	Cross-sectional	Neurobehavioral function	Taiwan
Tseng et al.[95]	Cross-sectional	Ischemic heart disease	Taiwan

included one that followed a large population during a seven year period. About 0.1 million people out of 7.3 million in the area evaluated had As-associated skin lesions. In addition, in small villages affected by As exposure, 30–40% of the population drinking the same As-contaminated drinking water had high As levels in urine, hair, and nails, but they did not have As associated skin lesions, indicating that sub-clinical effects may be more widespread than clinical effects. The authors found that families that had safe water for drinking and cooking during a 2-year period, but that had been previously exposed to As, still had high levels of As because of intake from food grown in contaminated areas and washing of food with contaminated water. Thus, if you minimize As contamination in drinking water, concentration of As in tissue still remains above normal, mainly due to consumption of food grown in contaminated areas.

Skin Lesions, Drinking Water and Urinary Arsenic

In a cross-sectional study in Bangladesh, Ahsan et al.[107] reported that 21.6% of participants in the study had skin lesions such as melanosis and/or keratosis. Of these subjects, 13.9% were currently drinking water with As levels less than 10 μg/L. This either points to previous higher-level exposures, or suggests that even levels below current guidelines are not safe. In a West Bengal study patients that had As-related skin lesions were using water with As levels of 800 μg/L, as a result, many patients with skin lesions also suffered from cancer.[77]

In addition, Ahsan et al.[107] underlined the fact that skin lesions were three times more likely in subjects with the highest levels of urinary As. This may be because urinary As is a cumulative exposure indicator, suggesting that urinary As concentration may be a good indicator for predicting negative health effects in humans.

Dose-Response Relationship between Arsenic Exposure and Chronic Health Effects

Smith et al.[108] reported that chronic health effects of inorganic As exposure in Northern Chile included As-induced skin lesions. Skin lesions were evident despite good nutritional status. Although previous generations have potentially been exposed to As in the Andes mountains, the dose-response link in the current generation was not influenced by As exposure of previous generations. Guo et al.[109] indicated that the prevalence of As dermatosis was highest in the regions that drank water from wells with higher concentrations of inorganic As. The prevalence of skin lesions was greatest in people over 40 years of age.

Kurttio et al.[110] reported that a significant increase in the risk of bladder cancer was seen at levels of As >0.5 μg/L in people from Finland.

This correlation was seen at exposure concentrations many times lower than any jurisdiction's current drinking water quality guideline. However, further research should be conducted to confirm this link.

Rahman et al.[111] indicated that there was a dose-response relationship between risk of hypertension and drinking water contaminated with inorganic As. The prevalence of hypertension increased in middle-aged men and in women over the age of 60 years. A clear dose-response link was shown as increased exposures were associated with increases in the prevalence ratio. Guha Mazumder[90] reported that chronic respiratory diseases increased significantly with increasing As concentrations in drinking water. Among clinical manifestations described were cough, crepitations (to make small sharp sudden repeated noises), and shortness of breath. In males, the prevalence of cough adjusted for age was twice as high as for females. With increasing As concentration in water, the prevalence of keratosis and pigmentation also increased. The association between exposure and response, and the prevalence of skin effects, were evident. In addition, in people already identified with skin lesions, the strongest correlation was with weakness, which increased with increased As exposure. The same link was confirmed by Milton and Rahman,[102] who showed that the prevalence ratios for chronic bronchitis increased with increasing As exposure. It appears that long-term ingestion of As may be a cause for chronic respiratory diseases and skin lesions.

ARSENIC IN HUMAN TISSUE

Drugs with Arsenic as an Ingredient

Homeopathic medicine is frequently used in countries such as India. In some cases, patients use non-doctor prescriptions containing As compounds to treat their disorder. As has caused health problems when used inappropriately and patients have represented with hyperpigmentation, keratosis, and increased As in tissues such as skin, hair and nails. This shows that people using As in homeopathic medicine may be at risk of toxicity and discouraging their use to be appropriate.[112]

Arsenic Accumulation in Tissues

Lin et al.[113] studied biomarkers in BFD patients in southwest Taiwan. Patients having BFD were linked with the presence of high concentrations of inorganic As (the most common As form) in well drinking water. A significant increase in inorganic As in urinary excretion, hair, and fingernails of BFD patients was observed, underlining that As in urine, hair, and fingernails are biomarkers of similar value when evaluating As exposure in humans.

In an Australian study by Hinhood et al.,[114] analysis of As in hair and toenails showed that there was a clear association with As in drinking water and residential soil. Their results also indicated that hair As concentrations were higher in people consuming greater amounts of As in drinking water than people exposed to As from other sources. Children had higher As concentrations in both hair and toenails compared with other age groups tested, probably because of more environmental As exposure from their daily life activities. The study also indicated that toenail As concentrations were more strongly linked with external As exposures than was hair As concentration.

In a separate study, Chakraborti et al.[115] showed that As levels were high in hair, nail, and skin tissue of individuals with As-associated skin lesions. However, As levels were also high in people that had no skin lesions, but who lived in the same villages in the Ganga-Meghna-Brahmaputra plain of India and Bangladesh. These individuals may not suffer from physical symptoms at the present time, but they may be sub-clinically affected. Skin lesions and use of biological markers like As concentration in hair and nails may help in early diagnosis of chronic As poisoning.

Urinary Arsenic Species

In studying BFD patients in Taiwan, Lin et al.[113] found that individuals using well-water contaminated by As excreted higher total urinary As. In studying the health effects to Mexican populations from chronic As exposure, Meza et al. [116] found a weak link between total As in water and total As eliminated in urine. Among the urinary As species, dimethyl arsenic (DMA), inorganic As (in the form of trivalent As) and monomethyl As (MMA) were most common. In this study, the methylated As metabolites, such as DMA, were excreted at a level of about 50%. This was considered a very low percentage of methylated As metabolites. Different communities that had experienced chronic As exposure did not have the same level of As metabolism, suggesting that the main reason may be individual ability to metabolize and excrete As due to ethnic differences such as the presence of native Indian, Mexican and Spanish mixture (genetic polymorphism).

Urinary Porphyrins

The impact of As among people who use As-rich coal for heating, cooking, and drying of food in poorly ventilated dwellings in Guizhou province, China was studied by Ng et al.[117] It was found that burning As-contaminated coal causes effects on porphyrin metabolism. The study indicated significant positive association between urinary As concentration and porphyrin concentration. Porphyrin levels were higher in the young, women, and old age groups compare to controls (<20, and >40), suggesting that people spending more

time indoors are at greater risk of increased As exposure, resulting in higher porphyrin levels. However, the most interesting finding was that younger age groups had higher levels of uroporphyrin and coproporphyrin III, which can be used as early biomarkers of chronic As exposure. Since As affects porphyrin excretion and the heme biosynthetic pathway, there is a need for further investigation into possible associations between urinary porphyrins and both As-induced cancer and non-cancer clinical manifestations.

ARSENIC EXPOSURE FROM FOOD

The study by Rahman et al.[77] in West Bengal, India, looked at other As exposure sources. The study revealed that consumption of food from contaminated areas was another source of chronic As poisoning, since food products like vegetables and rice were cultivated using As-contaminated groundwater. The level of As in groundwater used to cultivate rice and vegetables ranged from 103 μg/L to 827 μg/L. The average As levels in rice and vegetables were 0.323 μg/g and 0.027 μg/g. It was estimated that in villages where people consume such agricultural products, the mean daily individual exposure was about 100 μg. In addition, Chakraborti et al.[115] confirmed that contaminated groundwater used to cultivate vegetables and rice consumed by people may be an important pathway of ingesting As. Urinary As concentration in control subjects drinking "safe" water was higher than the norm, most likely as a direct result of contamination of food products.

Huq and Naidu[118] also suggest from their study in Bangladesh that food is another pathway of As exposure. Different foods have different As concentrations. However, there is uncertainty about the bioavailability and associated toxicity of As from different foods. Data from As concentrations in certain vegetables from where As poisoning is documented show that people using the same water source are not affected the same way. This raises the need for more investigation related to speciation and bioaccumulation of As.[118,119]

Rmalli et al.[120] investigated As levels in food imported from Bangladesh to the United Kingdom. Results showed that imported vegetables from Bangladesh have from 2-fold to 100-fold higher concentrations of As than vegetables cultivated in the United Kingdom, European Union, and North America. Average As concentrations found were for the skin of arum tuber, 540 μg/kg, arum stem, 168 μg/kg, and amaranthus, 160 μg/kg. The study did not determine the As species found in the foods, which is necessary to asses the risk to humans. This does, however, further support the fact that food may be an important route of As exposure in some regions and that such exposure could have long-term health effects in people.

Social Impact of Chronic Arsenic Exposure and Safety Caution

In their review of chronic As toxicity, Ratnaike et al.[15] stressed the impact of As contamination, not only on people's health, but also on the economy, personal incomes and crop productivity. Furthermore, Moyad[121] explained the importance of public awareness of As toxicity. As has not been routinely tested in Canada in the past, but the data in this review clearly show the need to test all groundwater supplies for As compounds, especially inorganic As. Populations most at risk are those using private well-water as a drinking water source. Frequently, such sources are only tested for coliforms and nitrates. Therefore, public education and groundwater monitoring are the most effective ways to provide people with needed information related to As and its negative impact on human health.

Mechanism of Arsenic Toxicity and Carcinogenicity

The detailed mechanisms of As toxicity and carcinogenicity are not well understood. Experiments in animals and in vitro indicate that As acts at the cellular level at low doses of exposure.[11] In reviewing the literature on As carcinogenicity, Kitchin[14] found that mechanisms of action included chromosomal abnormalities, oxidative stress, altered DNA repair, altered DNA methylation, altered growth factors, cell proliferation, promotion/progression, gene amplification, and p53 gene suppression. In addition, the author suggested that the methylation of inorganic As can actually be a toxification, not a detoxification pathway as methylated trivalent As metabolites play an important role in carcinogenesis.

In a study by Nesnow et al.,[122] it was stressed that DNA damage induced by methylated trivalent arsenicals is mediated by reactive oxygen species. Mass et al.[123] indicated that exposure of human lymphocytes to methylated trivalent As causes direct DNA damage. Their study suggested that As can be carcinogenic and/or genotoxic by direct and/or indirect changes in the structure of DNA and chromosomes. Mahata et al.[124] compared the As-induced cytogenetic damage between symptomatic (having skin manifestations) and asymptomatic individuals who drank As-contaminated water. Results indicated that the frequency of genetic damage was higher in symptomatic than asymptomatic individuals. In addition, using a sodium arsenite treatment in vitro, it appeared that lymphocytes of the control group were more sensitive than those of symptomatic or asymptomatic groups. The authors suggested that lymphocytes of people exposed to As for long periods of time reply weaker than the unexposed control group, which may be due to acquired susceptibility. Mahata et al.[13] suggested that the higher numbers of chromosomal aberrations occurring in lymphocytes was related to chronic As exposure, and cancer risks may be predicted by knowing in advance the predisposition to genetic alterations of this population group. Also, Mahata

et al.[13] and Yamauchi et al.[125] reported that after stopping As exposure, patients may have less frequent chromosomal aberrations, or DNA damage was reversible and returned to the previous state. Further research is needed to fully understand the biochemical and cytotoxic mechanisms of As toxicity.

Treatment of Chronic Arsenic Toxicity

There is no clear treatment for chronic As toxicity. The effectiveness of drugs was studied in clinical trials which showed that one form of chelation therapy can stop deterioration of chronic toxicity symptoms, while at the same time preventing outcomes such as cancer. Two main treatments were dimercapto succinic acid (DMSA) and 2, 3-dimercapapto-1-propanesulfonate (DMPS). The study indicated that DMSA did not improve the skin lesions in chronic arsenicosis patients. In contrast, DMPS improved significantly chronic arsenicosis.[90] In a separate study, Guha Mazumder et al.[126] found that DMSA did not improve patient health status, nor did it benefit patients with skin lesions from chronic arsenicosis. However, DMPS increased excretion of As in the urine several-fold.[127] Patients under this chelation therapy had significant improvements in symptoms. The increase in urinary As excretion during chelation therapy may be the key factor in DMPS therapy. Further research is needed to confirm the efficacy of this drug.

Guha Mazumder[90] indicated that proteins in food may increase the elimination of inorganic As by increasing methylation. Hence, people exposed to As are advised to increase protein consumption from both animal and plant origins. In addition, retinoids and antioxidants have anti-keratinizing effects and may prevent cancer. The study underlines that clinical presentations, like chronic bronchitis, interstitial lung disease, portal hypertension, peripheral vascular disease, and peripheral neuropathy, must be treated regularly, so that the patient's health will not deteriorate. Early detection of cancers due to chronic arsenicosis, especially skin, urinary bladder and lung, can improve the intervention and slow the progress of disease.

METHODS FOR ESTIMATING ARSENIC EXPOSURE IN HUMANS

A detailed review of the methods for evaluation of individual As exposure was recently compiled by Yoshida et al.[8] and is summarized below. Evaluations of As exposure among individuals are classified on the basis of: (i) monitoring As concentration in drinking water, and (ii) biological monitoring for As exposure.

Arsenic Concentration in Drinking Water

Four methods have been described for evaluating As exposure in humans based on As concentration in drinking water. The first method uses the

concentration of As in drinking water as an index of exposure, but it does not consider individual consumption volume. This reflects only current exposure that correlates with short-term effects, but provides less information about long-term effects. The second method seeks to establish the daily body burden of As from the amount of drinking water consumed. Air temperature and humidity may effect the daily individual consumption. The third method is based on average As exposure. This is an advanced index because it can assess the link between exposure and chronic health effects, such as cancer, occurring after long-term exposure. The last method is a cumulative As exposure index, which is more appropriate for cases where As levels in drinking water have changed, or where there has been a long period of low level As exposure.[8]

Biological Monitoring of Arsenic Exposure

Drinking water from wells can contain inorganic As in both the trivalent or pentavalent oxidation states.[8] Inorganic As is metabolized by two-step methylation and the total amount of inorganic As, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) can be used as biomarkers of As exposure. In one study, Styblo et al.[128] compared in vitro methylation of trivalent and pentavalent As. They concluded that trivalent arsenicals methylated more rapidly than pentavalent arsenicals.

In general, there are four main methods of As biomonitoring. The first method determines the concentration of As in voided urine. Calderon et al.[129] indicated that urinary As is a good index for estimating As exposure. As concentrations in urine were evaluated in a U.S. population that was exposed to inorganic As in drinking water in the range of 8 to 620 μg/L. The authors found a strong link between the concentration of urinary As and the concentration of inorganic As in drinking water. It was suggested that a few urine samples are able to evaluate the inorganic As burden an individual has received from drinking water. The second method measures the amount of As in blood. It is preferred to use peripheral blood samples for the evaluation of As exposure. Blood and urine samples reflect individual As intake and are not contaminated from external factors (dust, hands, contaminated water). The third method determines the amount of As in hair. Hair samples are used as a biomarker for As exposure because inorganic As and DMA are stored in the hair root and thus reflect past exposure. The last method is to estimate the amount of As in nails. Nails of fingers or toes are used as they reflect As storage 3 months ago in fingers and 6 months ago in toes. Hair and nails are used as biomarkers to estimate average As exposure.[8]

CONCLUSIONS AND RECOMMENDATIONS

The ingestion of As by humans can cause a variety of disorders, including skin lesions (e.g., hyperpigmentation, melanosis, keratosis), respiratory system problems (e.g., chronic cough, shortness of breath, bronchitis), nervous system effects (e.g., neuropathy, neurobehavioral, weakened memory, lower IQ, decreased attention), cancers of different organs (e.g., skin, lung, bladder), and reproductive effects (e.g., pregnancy complications, fetus abnormalities, premature deliveries, reduced birth weight). There are, in addition, potential links to heart disease and diabetes, but further evidence is needed to support these relationships. Approaches available to document chronic As exposure include analysis of As levels in drinking water, and measurement of urinary, nail, hair and blood As levels (biological monitoring). It has been shown that even low level As-exposures may affect human health, with greater effects in malnourished people. Recent evidence also implicates ethnic origin as a potential variable when determining As effects.

It is becoming clear that a drinking water quality guideline of 50 μg/L As is not protective, and while guidelines have decreased (to 25 μg/L in Canada and 10 μg/L USA and WHO), attempts to lower them to $\leq$5 μg/L (Canada) must be encouraged. Because groundwater can contain high levels of As, most groundwater sources used for drinking water should be tested for As. If total As concentrations are above 5 μg/L, then it is suggested that biological monitoring should be carried out. This includes measuring As levels in urine, blood, toenails and hair.

There are a few promising treatment methods currently in use, including chelation therapy, that may reduce or at least arrest deterioration of chronic As-poisoned individuals. At any one time, it is only a small percentage of a population that shows clinical symptoms, making it a prerequisite to test drinking water, and potentially humans, in order to prevent this element from causing systemic illness. In addition, education of the public about the consequences of drinking water contaminated with As is a necessity. Research needs include the improvement of As quantification in both water and human samples, as well as improving our understanding of the environmental occurrence and cycling of As. A key aspect is to develop a much better understanding of the relationship between chronic As exposure and various adverse effects (i.e., quantitative) in humans, and a better understanding of the underlying mechanisms of action (chronic toxicity). Unfortunately, rural water users have received little research and monitoring support from government agencies, corporations, and Non-Government Organizations. The on-going challenges to produce safe drinking water from typically poor quality rural water sources therefore continue to provide extreme challenges for communities and individuals that commonly have few resources available to them, even in developed countries such as Canada.

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