

Review Paper

Arsenic in the environment : Effects on human health and possible prevention

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Abstract: Arsenic is a major environmental pollutant and exposure occurs through environmental, occupational and medicinal sources. The contaminated drinking water is the main source of exposure and affected countries are India (West Bengal), Bangladesh, China, Taiwan, Thailand, Chile, Argentina and Romania. Concentrations of arsenic in affected areas are several times higher than the maximum contamination level (MCL) (10 µg/l). Arsenic exposure to human results in degenerative, inflammatory and neoplastic changes of skin, respiratory system, blood, lymphatic system, nervous system and reproductive system. There is no particular remedial action for chronic arsenic poisoning. Low socioeconomic status and malnutrition may increase the risk of chronic toxicity. Early intervention and prevention can give the relief to the affected population.

Key words: Arsenic, Drinking water, Maximum contamination level (MCL), Health effects, Intervention, Prevention

Introduction

Arsenic is semi metallic in nature and widely present in the earth-crust in the forms of oxides or sulfides or as a salt of iron, sodium, calcium, copper etc. Arsenic and its compound are well known for its toxicity and carcinogenicity. Individual exposures to arsenic from various sources like food, air, water, occupational settings and medicines. Contamination of arsenic in ground water is the global problem and millions of people are at a risk of arsenicosis. Contaminated ground water is the main source of exposure to inorganic arsenic to the human population. Bangladesh, India, China, Taiwan, Thailand, Chili, Romania are the major affected countries where inorganic arsenic present in the ground water with high concentration. The areas across the Gangetic plains in India and Nepal also recently reported as the area affected from it (Maharjan *et al.*, 2005). World health organization (WHO) and US environment protection agency (EPA) had set up the standard for drinking water known as MCL which is 10 µg/l. Drinking water with MCL or below to MCL is not hazardous to the population. Long-term ingestion of inorganic arsenic other than organic arsenic causes multisystem adverse health effects because organic forms are less toxic and rapidly excreted from body *via* urine. The clinical manifestations of chronic arsenic exposure are skin lesions, cardiovascular disease, neurological effects, chronic lung disease, cerebrovascular disease, reproductive disease, adverse renal affects, developmental abnormalities, hematological disorders, diabetes mellitus and cancers of skin, lung, liver, kidney and bladder. Low birth weight and adverse pregnancy outcomes are also documented by chronic toxicity of arsenic. Skin manifestation is the early feature of chronic arsenic exposure and cancer is the late phenomenon. Presence of both melanosis and keratosis are the conformational sign of chronic exposure of arsenic. Arsenic affect the human populations regardless of sex and age but the

children are less susceptible to arsenicism (Concha *et al.*, 1998; Chowdhury *et al.*, 2003). Chelation therapy is not effective in chronic toxicity. Thus prevention is better remedial action for chronic arsenic poisoning. People with well nourishment and good socioeconomic status are less susceptible to chronic toxicity.

Arsenic in the environment:

Arsenic is a naturally occurring ubiquitous element with metalloid properties. Arsenic is highly mobilized element and mainly cycled by water in the environment. Arsenic is widely present in soil, rocks, sediments and metals ores in the form of oxyhydroxide or sulfide or compounds of various metals in the most part of world (Aronson, 1994). Human population is mostly exposed to arsenic through ingestion, inhalation and dermal contact. Ingestion of arsenic contaminated water, foods, drugs, wines, smoke of cigarette and fossil fuels are the various routes of arsenic exposure to the population both acute and chronically (NTP, 1999). In occupational exposure, the workers are exposed to airborne arsenic from the industries of smelting and refining metals, producing and using arsenic-containing chemicals, manufacturing of glass, semiconductors and various pharmaceutical substances (USPHS, 1989). In medicinal exposure to arsenic, some arsenic containing drugs historically and presently are used to treat some diseases like syphilis, asthma, rheumatism, cough, pruritus and itching (Wong *et al.*, 1998; Ko, 1999). Pentavalent arsenic is used to treat advanced trypanosomiasis and acute promyelocytic leukemia (APL) is treated with arsenic trioxide (Novick and Warrell, 2000; Soignet *et al.*, 1998). In seafood, arsenic present in its organic form with elevated concentration, which are considerably less toxic than inorganic arsenic (ATSDR, 1998). Drinking water is the primary and main route of exposure to arsenic. MCL is the standard concentration of arsenic in drinking water which is not hazardous, is set by the US EPA that is 10 µg/l (EPA, 2001) and the guideline

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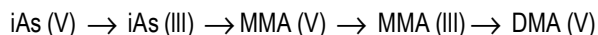


value for concentration of arsenic in drinking water is recommended by the WHO is also 10 µg/l (WHO, 1992). Millions of people are compelled to use the drinking water with higher arsenic level than MCL worldwide. West Bengal (India) and Bangladesh are the worst affected areas in the world from arsenicism. The standard of most developing countries is 50 µg/l, which is several times higher than the MCL and more hazardous to the population. It is necessary to reset the standard in these countries. In West Bengal (India), the arsenic concentration in drinking water is about 60 to 3700 µg/l and about 40 million people are affected from it (Acharyya, 2002). In middle Ganga plain, Bihar, 206 tube wells (95% of total) were analysed for arsenic content and showed that 56.8% tube wells have exceeded arsenic concentration of 50 µg/l and 19.9% have more than 300 µg/l (Chakraborti et al., 2003; Acharyya et al., 1999). In Bangladesh, more than 70-80 million people are at a risk of drinking contaminated water. The drinking water arsenic levels were ranged from nondetectable to 4700 µg/l (British Geological Survey, 2001). In Chile, the arsenic level in drinking water was very high and about 750 to 800 µg/l, which caused several skin and lung disease (Smith et al., 2000). In Taiwan, the arsenic concentration in well water used for drinking purpose were 10-1800 µg/l and a peripheral vesicular disease called "Black foot disease" is a common disease among the living population due to arsenicism (Tseng et al., 1995; WHO, 2003; Lamm et al., 2006). In Romania and Hungary, the range of arsenic concentration was 2 to 176 µg/l and about 4,00,000 population used drinking water above MCL and suffered from adverse health effects of arsenicism (WHO, 2003). In Argentina, the concentration of arsenic in groundwater ranged from 100 to 2000 and about 200,000 people use the contaminated water (British Geological Survey, 2001). In China, the concentration of arsenic in well water in the affected areas was 50 µg/l to 2000 µg/l and about 2 millions people in the affected area use the drinking well water containing arsenite more than common standard, which cause Raynaud's disease in the population. The patients of Raynaud's disease suffered from increasing the resistance of blood vessels and reduced the speed of blood flow in the extremities (Xia and Liu, 2004; Yu et al., 2000). In New Hampshire, USA, inorganic arsenic was present in about 95% sample of drinking water and the concentration was from 0.01 µg/l to 180 µg/l (Peters and Blum, 2000).

Metabolism of arsenic:

Biotransformation is the major metabolic pathway for inorganic arsenic (iAs) in humans and in most of the animal species. The chemical speciation of inorganic arsenic is important for health effects. Toxic inorganic arsenic species can be biomethylated by bacteria, algae, fungi, invertebrate and humans to yield monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) which are less toxic than inorganic arsenic. Methylation of inorganic arsenic mainly occurs in liver but other organs also have the arsenic methylation activity (Vahter, 2002). In this process inorganic arsenic is enzymatically biotransformed to methylated arsenicals including MMA and DMA, these are the

end metabolites and the biomarker of chronic arsenic exposure (Biggs et al., 1997; Thomas et al., 2001).



Firstly, reduction of iAs (v) to iAs (III) is mediated by glutathione, acts as reducing agent and then methyl group is transferred to iAs (III) from S-adenosyl methionine to form MMA (V). Then MMA (V) is reduced to form an intermediate metabolite monomethylarsonous acid (MMA^{III}) in methylation process and during the second methylation, MMA (III) is oxidized to DMA (V) (Le et al., 2000; Thomas et al., 2001). Glutathione and S-adenosyl methionine acts as co-substrate (Styblo and Thomas, 1995). The activity of first methylation step is represented by the ratio of iAs / MMA, if the ratio is high which indicate poor methylation and activity of second step is denoted by the ratio of MMA / DMA, if the ratio is low which indicate good methylation (Del Razo et al., 1997; Vahter, 1999). Children are poor methylator and good excretor in comparison to the adults. Thus children are less susceptible to arsenicism (Concha et al., 1998; Chowdhury et al., 2003).

Toxicity of arsenicals

Biomethylation is initially detoxification and deactivation process of toxic arsenic species. Methylated end products of inorganic arsenic are MMA (V) and DMA (V) that are excreted in urine as the biomarker of chronic arsenic exposure, but not MMA (III). MMA (III) is the intermediate product in methylation process. The toxicity of arsenicals include arsenite (III), arsenate (V), MMA (V), DMA (V) and MMA (III) are determined by using the criteria of leakage of lactate dehydrogenase (LDH), intracellular potassium (K⁺) leakage and mitochondrial metabolism of tetrazolium salt in change human hepatocytes (Petrick et al., 2000, 2001). The order of toxicity of arsenicals is:



In arsenic biotransformation the intermediate product monomethylarsonic acid (MMA^{III}) is highly toxic than other arsenicals, which might be responsible for the arsenic-induced carcinogenesis and other effects (Styblo et al., 2000). Thus the methylation of arsenic is considered to be an activation process, not a detoxification.

Human health effects:

Chronic ingestion of inorganic arsenic causes multisystem adverse health effects. High dose of arsenic in drinking water causes characteristic skin manifestation, vascular disease including arteriosclerosis [Peripheral vascular disease and ischemic heart disease (ISHD)], renal disease, neurological effects, cardiovascular disease, chronic lung disease, cerebrovascular disease, reproductive effects and cancers of skin, lungs, liver, kidney and bladder. Increased exposure of arsenic is also associated with non insulin dependent diabetes mellitus (Rahman et al., 1998; Wang et al., 2003). High arsenic level in drinking water affected the visual perception of children but not

the visual motor integration, are confirmed by visual-motor integration test (VMIT) and motor free visual perception test (MVPT) (Siripitayakunkit *et al.*, 2000a). Arsenic exposure from drinking water was associated with reduced intellectual function of children in Bangladesh. In dose-response manner, the children who use the drinking water with high arsenic concentration ($>50 \mu\text{g/l}$) execute lower performance than those children, using drinking water with low arsenic ($<5.5 \mu\text{g/l}$) (Wasserman *et al.*, 2004). Arsenic is also associated with the growth retardation in children. The height of children might be affected by the arsenic in drinking water. The children who have high arsenic concentration in their hair had less height than the children with low arsenic (Siripitayakunkit *et al.*, 2000b). Arsenic contaminated drinking water is also responsible for spontaneous abortion, stillbirth and infant mortality (Aschengrau *et al.*, 1989; Rich *et al.*, 2000).

Effects on skin:

Skin manifestation is the most common and initial sign of chronic arsenic exposure. Chronic ingestion of arsenic causes characteristic melanosis, keratosis, basal cell carcinoma and squamous cell carcinoma (Maloney, 1996). Presence of both melanosis and keratosis is the conformational sign of chronic arsenic toxicity. Melanosis includes diffuse melanosis (hyperpigmentation), spotted melanosis (spotted pigmentation), non melanoma (depigmentation) and leucomelanosis in which white and black spots side by side present on the skin. Melanosis is found mainly on the trunk and extremities or on the whole body (Guha Mazumdar *et al.*, 1988). Characteristic rain drop pattern, another skin manifestation is a result of hypopigmentation (Smith *et al.*, 2000). Keratosis is a late feature of arsenical-dermatosis, especially appear on palm and sole in different manner such as discrete or nodular keratosis, spotted keratosis (Mazumdar *et al.*, 1998) and combination of nodular and spotted keratosis is known as spotted palmoplantar keratosis (Chowdhury *et al.*, 2000). Depigmentation an arsenic-induced skin lesions has the increasing risk of low-grade basal cell carcinoma (Abernathy *et al.*, 1999) and Bowen's disease. Bowen's disease is a precancerous lesion and predisposed to an increased incidence of other malignant lesions (Graham and Helwig, 1959, 1966). Chronic ingestion of inorganic arsenic has also been associated to the development of squamous cell carcinoma (Centeno *et al.*, 2000). The long-term ingestion of arsenic lead to accumulate in keratin rich areas of body and appears as white lines in the fingernails and toenails, called Mee's lines (Fincher and Koerker, 1987). Dermatitis instead of characteristic melanosis and hyperkeratosis of palm and sole were mostly found in the workers of smelting industry due to the local irritation caused by high concentration of airborne arsenic (Pinto and McGill, 1953). In West Bengal (India) and Bangladesh, about 80% of people use the high level arsenic drinking water which can cause hyperpigmentation, hyperkeratosis and painful skin blisters. The latency period of skin lesions for arsenic after first exposure, was 23 years. (Guha Mazumdar *et al.*, 1998; Haque *et al.*, 2003).

The males show higher prevalence rate of arsenic-induced skin lesions than females with clear dose response relationship. These research studies showed that the high rate of prevalence in affected area is an indication that future is in danger (Tondel *et al.*, 1999). In Inner Mongolia and China, a study was conducted for the relationship in between arsenic in ground water and the skin manifestations. It was reported that the concentration of arsenic in water was ranged from 50-1354 $\mu\text{g/l}$ and prevalence of skin lesion was 44.80%. The persons of above 40 years of age showed the highest rate of prevalence of skin-manifestations without sex differentiation (Guo *et al.*, 2001).

Effects on respiratory system and lung:

An affect of inorganic arsenic in the form of airborne particles (mostly arsenic trioxide) on respiratory system mainly occurs in industrial area. Initially, the lesions of mucous membrane of respiratory system including the irritation of nasal mucosa, larynx, bronchi and later perforation of nasal septum were observed (Hine *et al.*, 1977). Exposure to inorganic arsenic in crude and refined form causes rhino-pharyngo-laryngitis, tracheobronchitis and pulmonary insufficiency due to emphysematous lesions (WHO, 1981a). Exposure of arsenic through other routes instead of inhalation can also affect the respiratory system and cause a high rate of chronic cough and bronchopulmonary disease (Borgono *et al.*, 1977). In West Bengal and Bangladesh, the prevalence rate of cough, shortness of breath and chest sound (crepitations and rhonchi) in lungs of both males and females were found to increase with age and with increasing the concentration of arsenic in water. Prevalence odd ratio (POR) were increased for those persons who had arsenic-induced skin lesions and used the drinking water of high arsenic concentration ($> \text{or} = 500 \mu\text{g/l}$), in the comparison of the persons who had normal skin and used the water of low arsenic concentration ($< 50 \mu\text{g/l}$) (Mazumdar *et al.*, 2000; Milton and Raham, 2002).

Carcinogenic agents are classified as either genotoxic or non-genotoxic. Inorganic arsenic is indirect-genotoxic carcinogen of lungs, skin and several internal organs in the humans (IARC, 1987). Inorganic arsenic is weak to induce gene mutation at specific loci. The biochemical action of inorganic arsenic carcinogenicity include inhibition of DNA repair enzyme (DNA Ligase enzyme), inhibit DNA methylation, interference with tubulin dynamics and mitosis, induction of oxidative stress, and promote cell clone immortalization (USEPA, 1997). The genotoxicity of inorganic arsenic includes both structural and numerical chromosomal abnormality, increase in sister chromatid, gene amplification, and cell transformation (Waner *et al.*, 1994; Hsu *et al.*, 1997). Thus arsenic is probably a promoter or progressor rather than a true carcinogen (IARC, 1987).

Arsenic has been associated with lung cancer to the workers of manufacturing unit and peoples linked with the industries of arsenic containing pesticides, chemicals and metals smelting area. The trivalent (As^{III}) form of inorganic arsenic has



shown the activity of carcinogenesis. Exposure to 50 µg/l airborne arsenic (mostly arsenic trioxide) to the person for a long period about 25 years would increase the 3-fold lung-cancer mortality (WHO, 1981b). In Northern Chile, in a case control study, patients of lung cancer between 1994 to 1996 were diagnosed with drinking water source and cigarette smoking. 152-lung cancer case and 419 controls were found in the relationship between lung-cancer and arsenic. Synergism between cigarette smoking and ingestion of arsenic drinking water were found. Smoking and chronic obstructive pulmonary disease (COPD) increases the cases of lung cancer mortality (Ferrecio *et al.*, 2000). In Chile, a Standard mortality ratio (SMR) for lung cancer was for men 3.8 and for women 3.1 in between the 1989 to 1993 (Smith *et al.*, 1998). In Bangladesh in 2000 for estimation of arsenic-induced health problems especially lung cancer showed that the lifetime risk of lung cancer to males were 159.1 and 23.1 for females per 100,000 populations (Chen and Ahsan, 2004). In Thailand, the data of 5-year (1994-1998) arsenic contamination showed prevalence of lung cancer and reported the highest proportion of lung cancer about 10.2 percent from cancer registry (Choprapwon and Porapakkham, 2000). In 243 township of Taiwan, about 37,290 cases of lung cancer was observed in which 26,850 patients were males and remaining females, in between the period of 1981-1999 (Guo *et al.*, 2004). These data's of lung cancer cases are suggestive of carcinogenicity of arsenic and its species.

Effects on nervous system:

The major target organ of toxic effects of heavy metals like arsenic, mercury and lead, is central nervous system. The adverse effects of chronic exposure to drinking arsenic water on nervous system are reversible peripheral neurological damage. Exposure to inorganic arsenic for a long period can cause the peripheral neuropathy, which is similar to the Guillain-Barre syndrome [(aponeurotic reflex) (Goddard *et al.*, 1992)]. The other effects of exposure are change in behaviors, confusion, disorientation, memory loss and cognitive impairment. Chronic ingestion of arsenic contaminated water is increasing the prevalence rate of cerebrovasculer disease especially cerebral infarction (Chiou *et al.*, 1997). Cases of arsenic-neuropathy that were found in USA (Heyman *et al.*, 1956) and Japan (Oida, 1957; Hara *et al.*, 1968) are caused by occupational exposure to arsenic spray and arsenic at a copper refining industry. The workers were suffered from peripheral nervous disturbances and neuritis retrobulbaris as well as chronic rhinitis combined with septum perforation. In Czechoslovakia, an exposure to inorganic arsenic is responsible for the hearing losses in the children. In a group of 10-years old 56 children, living near a power plant burning coal area and had high arsenic content in water, were compared with a control group of 51 children of same age. The suffered children had significant hearing losses in both air and bone conduction at a high frequency rate (Benko *et al.*, 1977). In China, a case-control study was made between 57 person with arsenic-induced skin lesions and are found to use the arsenic drinking water for a

long period. The study demonstrated that the exposed persons got various types neurological disorders including abnormal distal sensation, abatement of temperature sensation and pressure abatement, vegetative nerve functional lesions such as hypohidrosis (diminished perspiration), adiphoresis (absence or deficiency of perspiration), in the comparison of normal person (Zhang *et al.*, 2000). A 10 year study conducted in affected area of West Bengal and the report documented that the 37.2 percent patients of arsenicosis were suffered from arsenical neuropathy with the affliction of sensory and motor nerves (Chowdhury *et al.*, 2000).

Prevention

The essential and basic efforts for the reduction of chronic arsenic toxicity are prevention. Prevention is better than cure. Many countries have focused on arsenic health effects and prevention. In recognition of the seriousness of the problem of arsenicosis among large population worldwide and there is no effective treatment. We are interested in increased preventive efforts not only because of significant impact on the population at risk, but also because of the other conditions associated with the continued arsenic exposure in drinking water.

Primary prevention:

Due to low socioeconomic status of the large population of affected area, it is not possible to eliminate total arsenic and to afford the arsenic free drinking water to everyone. Thus it is suggested to use alternative water source such as rainwater or to remove the arsenic from contaminated water. The most important remedial action for the person who suffered from arsenicosis, the first major priority is preventing the use of arsenic contaminated drinking water to stop further exposure or providing the arsenic free drinking water or drinking water with arsenic below to the MCL of WHO and USEPA, that is 10 µg/l, to impede the future exposure. The second one is distinct the high and low arsenic source of drinking water and aware the population to use the low arsenic water (below MCL) for drinking purpose and high arsenic water for other purposes. Encouragement to the suffered persons and give them the education about the adverse health effects of arsenicosis and its prevention by dietary supplements that help to decrease the future exposure. The affordable, efficient, low maintenance and household technologies/ instrument such as low cost filtration systems and iron hydroxide precipitation for removal of the arsenic from contaminated water, for the population of affected area, could be made available by the local administration.

Secondary prevention:

For the reduction of toxicity and elimination of metals from the body, chelating agents are generally used. In acute arsenic toxicity, chelation treatment is a good remedial action to reduce the toxicity and for elimination. The most common antidote for arsenic and other metals poisoning is British anti-leusite (BAL), chemically 2,3-dimercaptopropanol. BAL is an efficient antidote

in acute poisoning but it also has toxic activity. Thus due to its toxic activity BAL are less used as antidote. Presently thiol chelators like meso 2,3-dimercaptosuccinic acid (DMSA), sodium 2, 3-dimercaptopropane-1-sulfonate (DMPS) and monoisoamyl DMSA (MiADMSA) are commonly used, in both acute and chronic arsenic toxicity. DMPS has the efficacy to increase the removal of most arsenic species from urine (Domingo, 1995). DMPS forms the complex with MMA (III), which is most toxic intermediate arsenicals in biomethylation and rapidly remove it via urine. Oxidative-stress is also caused by chronic toxicity. For reducing to it MiADMSA is successfully administrated in experimental animals and recently it is also used with the combination of antioxidants to increase the potency.

Tertiary prevention:

Safe drinking water and well-nourished food is essential for the prevention of chronic arsenic toxicity. Balance nutritious-supplements play a major role in the prevention of chronic arsenic poisoning. The diet with low protein, fats, vitamins and minerals may increase the risk of arsenic-induced skin lesions and other malignant disease. Deficiency of protein, folate and vitamin B in diet affected the biotransformation of arsenic by which arsenic is not excreted from body and causes its adverse health effects. Micronutrients like calcium, iron and zinc are reducing the arsenic toxicity by interacting it at the primary site of action. Deficiency of vitamins and antioxidants increases the reactive oxygen species (ROS) in the body that is leading to cause tissue damage and other harmful effects. A 10 year fieldwork were done in West Bengal (India) and Bangladesh in 1989-1999 had suggested that malnutrition may be responsible for skin lesions. Low nutrient diet may cause the skin lesions to the persons who use low arsenic drinking water, but high arsenic in drinking water (about 400 µg/l) may not cause the skin lesions to the persons with well-nourished food (Chowdhury *et al.*, 2000). Good nutrition and safe drinking water can remediate the melanosis and decrease the keratosis. Various reports suggested that population with good nutrition is less susceptible to arsenical disease. Functional food jaggery as dietary supplement prevented the arsenic induce toxicity thus it could be helpful for human population exposed to arsenic contaminated drinking water (Sahu *et al.*, 2006).

Future perspectives

Effective legislation, regulation and identification of the areas where the excess level of arsenic is found in drinking water are necessary. Failure to control the exposure from high MCL arsenic water will lead to future cases of arsenicosis.

Exposure monitoring and possible intervention for the reduction in further exposure of arsenic can reduce the arsenic toxicity and a significant step towards prevention. National and international co-operation is needed to develop effective strategies for arsenic toxicity prevention.

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