Journal of
Environmental & Analytical Toxicology

Tantry et al., J Environ Anal Toxicol 2015, 5:6
DOI: 10.4172/2161-0525.1000327

Review Article Open Access

Arsenic Exposure: Mechanisms of Action and Related Health Effects

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Abstract

Arsenic represents a natural drinking water contaminant that can deteriorate health due to its extreme toxic nature. Infant mortality, neuropathies, liver disease, cancer, eye diseases, cardiovascular disease and different skin alterations can stem from chronic arsenic exposure. The predominant species of arsenic comprise of arsenite and arsenate. Arsenite is more toxic in nature as compared to arsenate. Arsenic pollution is mainly caused by natural process such as weathering of rocks and minerals followed by leaching and industrial activities that lead to contamination of soil and groundwater. The WHO guideline permits the maximum limit of arsenic as 10 µg/L in drinking water. This review provides a comprehensive overview on arsenic mode of action, its sources and health related effects. The effect of toxicity, biomarkers of arsenic toxicity and the mechanism of arsenic dangers on humans are also discussed.

Keywords: Arsenic health effects; Arsenic; Cancer; Arsenic metabolism; Chronic arsenic exposure; Drinking water

Introduction

For many centuries, Arsenic (As) has almost exclusively been connected with deliberate poisoning, but in the contemporary world, it has largely contributed to escalating environmental pollution. The widespread anthropogenic use of pesticides containing arsenic can adversely affect human health. In addition, the activities that involves mining and burning of coal, thereby releasing it in the air has received pivotal attention [1]. Arsenic differs in its form when food and drinking water are concerned. In food, arsenic is found in both organic and inorganic form, depending on the kind of food, whereas, arsenic is present in inorganic form (either as As^{III} or As^{V}) in drinking water [2]. Groundwater usually contains arsenic as detected in 70 countries worldwide that has affected 140 million people. Most of the affected people live in Asia (such as Bangladesh, India) who have been affected with concentration levels higher than the WHO drinking water arsenic value of 10 µg/L as well as the national regulatory standards (e.g., 50 µg/L in India and Bangladesh) [3,4].

Arsenic contamination prevalent in groundwater often stems from geological sources and its consumption can cause chronic health disorders in numerous affected regions across the globe [5]. In Asia, arsenic found in groundwater is considered as the largest environmental health disaster that aims to threaten at least 100 million people in the Bengal Basin of Bangladesh and West Bengal. Arsenic exposure and consumption has been affecting India with cancer disease and other As-related ailments [6]. Arsenic is the 52nd out of 92 elements that is heavily found in earth's crust and has a concentration of 1.8 parts per million. This poisonous element occurs naturally in numerous minerals such as arsenopyrite, tennantite (copper arsenic sulfide) and realgar (arsenic sulfide). In soils, mostly the inorganic forms of arsenic are found such as As^{III} (arsenite) and AsV (arsenate) [7,8]. Monomethylarsonic acid (MMAA), Methylated species, trimethylarsine oxide (TMAO) and dimethylarsinic acid (DMAA) are vastly present in biomass, but soils also incorporate them [1]. In addition, As^{V} and As^{III} can be evaporated at regular temperature for transforming into arsine, MMAA changing to tomonomethylarsine [9], TMAO transforming to trimethylarsine (TMA) and DMAA taking shape of dimethylarsine (DMA) [10].

Different soil parameters are likely to affect the toxicity and bioavailability of arsenic prevalent in soil. Soil parameters such as redox potential, pH, soil and site hydrology can highly influence the toxicity of arsenic. In addition, microbial and plant components can affect the arsenic absorption. The above-mentioned parameters can affect the behavior of soil colloids and absorption capacity, thereby changing the bioavailability and solubility of arsenic [11-13]. In natural ecosystem settings, the chemical processes can play a pivotal role in controlling the arsenic exposure and mobility. However, there are increased chances that microbial metal reduction can also play an essential role in mobilizing toxic metals that can have disastrous effects on living beings' health. Microbial reduction of As^{V} and more poisonous and mobile As^{III} species can take place through respiration processes [14,15].

Numerous bacteria contain the As^{V}-reductase gene that is involved in As^{V} reduction [16], only few microorganisms which have the capability to respire As^{V} have been secluded [17]. The AsV-respiring bacteria are likely to use various electron donors such as hydrogen and acetate; and can be of different types ranging from mesophiles to extremophiles [17]. Through laboratory studies, it has been determined that microbial phenomena that plays an essential role in reducing and mobilizing As^{V} are more rapid as compared to inorganic chemical changes [18]. Laboratory researches revealed that these microorganisms can significantly contribute in As cycling in the earth crust [14,18,19].

Arsenic Mechanism of Action and Related Health Effects

Arsenic metabolism

Arsenic can enter human body by drinking impure water and can act as deterrent to secure health. Hence, arsenic is vulnerable to human health and can cause cancer also. This issue is becoming a

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Received August 17, 2015; **Accepted** October 25, 2015; **Published** October 28, 2015

Citation: Tantry BA, Shrivastava D, Taher I, Tantry MN (2015) Arsenic Exposure: Mechanisms of Action and Related Health Effects. J Environ Anal Toxicol 5: 327. doi:10.4172/2161-0525.1000327

significant health concern across the globe [20]. According to a current comprehensive study conducted by the genome-wide association, particular genetic differences connected with vulnerability of forming skin lesions were identified. It was also discovered that the arsenic metabolism differs in each individual [21]. Different methods have been developed that can benefit mammals in detoxifying inorganic AS. Although numerous organisms possess the capability to change inorganic As into organic arsenic, but liver arsenite methyltransferases is absent or deficient in certain mammals such as chimpanzee, guinea pig, marmoset monkey and various South American monkeys [22].

There is a major confusion regarding the appropriateness of methylation as the primary way to detoxify inorganic As^{III}. Various tissues prevalent in the methylation process of enzymes are diverse in nature. In case of mouse, its testis is the most active part as compared to kidney, lung and liver [22,23]. Hence, this depicts that inorganic As^{III} methylation process is not only reliant on liver, as understood in the past. Application of the product formed from reaction of a metal ion DIMAVAL (2, 3-dimercapto- 1-propanesulfonic acid) on 24 subjects in Chile played a significant role in changing DMA and MMA excretion in the urine. Hence, urine was affected by the use of chemical. Before DIMAVAL, the MMA excretion accounted for 14% but MMA escalated to 42% of total As excretion after oral administration [22]. Researchers also discussed the differences in As metabolism found in humans due to the fact that all groups of humans were aware of methylate inorganic As [24].

Researchers suggest that the significant factors that can influence As methylation will be required in future. It must be taken into consideration that the patterns of As organic compounds in urine substantially differ from one individual to others. For instance, a small number of females in the Argentina Andes excrete small quantity of MMA in their urine [25]. Methylation holds immense significance in relation to As metabolism phenomena, methylation reactions that consists of interactions, selenium and inhibitors, this encouraged the discussion of As interactions in the studies. This is significant because As and selenium differ in numerous biologic systems. Moreover, numerous investigators do not consider that the different ways prevalent for mammals to engage in methylation process and they ignore the multifaceted interactions and relationships of these ways. Research depicts that different human responses have been observed to As exposure in South America [25]. The differences in human responses when exposed to AS have been increasing with the passage of time and might require new techniques and different approaches of analysis. A significant technique is to use pharmacokinetic (PK) approaches on which intake of As (V), As (III), DMA, MMA and any combination of these four substances in the human body is based [26]. These approaches are used to illuminate tissues of As species that function according to change in dose and time. The PK approach has been used as model for testing a receptor-mediated system for inorganic As. Moreover, the researchers focused on examining the potential significance of complexity and differences in As toxicology. It must be taken into consideration that the typical molecular biology and biochemical research studies about how As metabolism takes place are insufficient.

Molecular processes of cancer formation

Arsenic is considered as an element that can cause cancer in skin, bladder, lung, liver, and kidney. Research has revealed that arsenic-related deaths can result from lung cancer [27]. Arsenic is not involved in causing gene mutations, thereby indirectly reacting with DNA (Figure 1). Numerous mechanisms have been established by which

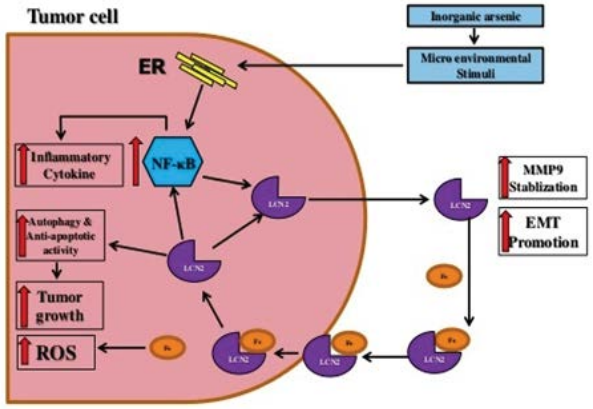

Figure 1: Long term exposure to inorganic arsenic associated with DNA hypermethylation which leads to the downregulation of tumor suppressor genes.

arsenical compounds form tumors such as genotoxic can damage, oxidative stress and abnormalities in chromosomes [20]. People that possess p53 Arg/Arg genotype were less prone to inorganic arsenic and had increased amount of DMA. This implies that they were better able to undergo arsenic methylation process and reduce toxification [28]. Arsenite cannot impede any DNA repair enzyme, but it is probable that arsenite can obstruct the management of DNA repair process as compared to the repair substances [29]. Aneuploidy can be subjected to arsenite. Arsenite is different from spindle poisons because arsenite does not hinder to form spindle fiber; instead arsenite is involved in deranging the spindle equipment through facilitating polymerization of microtubule.

While working on a latest cell conversion arrangement (by experimenting on rat liver epithelial cell line TRL 1215), it was discovered that global DNA epigenetic changes, initiation of the proto-oncogene c-myc and reduced DNA methylated enzymes activity significantly influenced the persistent exposure to harmful arsenite conversion. The findings of the research study explained that arsenite can act as a cancer-causing element through inducing hypomethylation of DNA, thereby causing abnormal gene characteristics [30]. Another experiment that was conducted on p53 promoter in human lung A549 carcinoma cells showed that opposite results can appear on DNA methylation process through arsenite. A long-standing subjection to arsenite escalated CpG methylation within the p53 promoter that had increased chances of blocking transcription of the significant p53 gene [31]. The p53 gene is considered as an important gene that subdues tumors and its protein product are vital in controlling the apoptosis, cell cycle and DNA repair. After 24 hours of conducting treatment with arsenite, the researchers observed significant changes in the p53 gene and the cell cycle in three cell lines. An effect of transfecting mutant p53 gene with cells depicted that the cells are more sensitive to arsenite.

Arsenic related health consequences

Childhood cancer: In theory, there is inadequate information related to arsenic subjection in drinking water that can cause the ailment of childhood cancer [32] described that arsenic can increase the chances of lymphoblastic leukemia risk; however the arsenic amount in usual drinking water was very low that deterred increase chances of Leukemia [33]. Increased levels of arsenic in Drinking water can cause bladder cancer bladder, skin cancer and can adversely affect the

intellectual ability of children [34]. Childhood cancer frequency rates in Nevada were observed at increased water levels in the range of 35-90 μg/L. The relative risk estimate was 1.25 (CI 0.91-1.69) for childhood cancer and 1.37 (CI: 0.92-1.83) for the vulnerable ailment of leukemia.

young children aged under 20 years, who were exposed to high arsenic content (RR=10.6, 95% CI 2.9-39.2, $p<0.001$) in drinking water became victims of mortality subject to liver cancer [35]. The affected children died prior to 1980 and the reason for their death could not be proved by any medical records nor was it confirmed that these children died because of increased exposure to arsenic in drinking water [33]. In short, it can be epitomized that past research studies rejects the notion that deaths are increasingly caused due to childhood cancers, but through one study, increased relative risks for liver cancer have been found that are subject to increased arsenic substances in drinking water.

Decreased infant weight and increased infant mortality: Arsenic exposure has a strong connection with increased infant death incidences and; according to certain research studies arsenic exposure can result in stillbirth and abortion [36], as well as decreased weight of new born babies [37]. Early-life arsenic exposure can highly weaken the neurological capabilities of children such as verbal communication abilities, IQ levels of girls are inversely related with arsenic exposure [38,39]. Birth weight differs according to countries such as decreased weight of new born babies resulting from low exposure to arsenic have been discovered Chile (28), Taiwan (86) and Bangladesh (28). In Chile, the decrease in average weight of new born babies estimation accounted for 57 g and 30 g in Taiwan. In Bangladesh, regression coefficients helped in understanding that an increase in 1 μg/g in hair arsenic can reduce babies weight upto 19.5 g [40-42].

Adverse effects on alterations: When arsenic is consumed by the human body, it causes pigmentation changes in the skin of the trunk and limbs and nodular keratosis on the soles and palms [41]. Through analyzing several epidemiological studies related to skin lesions, it was discovered that most people suffering from skin lesions had consumed drinking water containing arsenic content of >100 μg/L, although lesions have been reported at arsenic concentrations of <50 μg/L. In most populations involved in consuming drinking water and encountering arsenic water issues, lesions were considered as the first symptom to identify the issue. According to a current report from the Health Effects of Arsenic Longitudinal Study (HEALS) prospective study, the vulnerable risk of subjecting to skin lesions was not reduced after decrease in arsenic exposure for up to several years. Hence, lesions are likely to occur on skin several years after exposure reduces [43]. In 1960's, it was discovered that there is a high propensity of skin lesions to emerge due to arsenic content in drinking water in Taiwan [44] and the same results were revealed in India and West Bengal in the 1980s [45].

Human prostate cancer: In the late 1980s, the first evidence that inorganic arsenic was highly correlated with human prostate cancer discovered from Taiwan [46]. This was a follow-up study that concentrated on dose–response relationships between arsenic and cancer in a population exposed to high levels of arsenic in the drinking water from local artesian wells. The population studied belonged to the area of endemic "black foot" disease prevailing in southwest Taiwan, a disease that involved the peripheral vascular dysfunction likely due to arsenic exposure [47]. Although the original study had not looked at cancer of the prostate [47], the subsequent study identified a noteworthy correlation between arsenic vulnerability and prostate cancer mortality in this population [46].

Arsenic-induced diseases affecting eyes: A methodical survey had been conducted for determining whether chronic arsenic ingestion can result in any particular eye problems. It was discovered that exposed individuals suffered from watering, irritation, and redness in both eyes. Few populations also reported that they were suffering from conjunctivitis due to chronic arsenic ingestion [48]. A skilled ophthalmologist carefully screened the participants for conjunctivitis disease and related eye diseases. Some cases associated with having record of mucopurulent discharge (characteristic of bacterial conjunctivitis), photophobia and extreme watering (characteristic of viral conjunctivitis), and severe itching and ropy discharge (characteristic of allergic conjunctivitis) were exempted. Other symptoms due to arsenic exposure incorporated the pigmentation in the sclera, pinguecula, pterygium and conjunctival congestion.

Cardiovascular ailment: Epidemiological studies conducted across different parts of the world relating to high levels of arsenic (>300 μg/l) in ground water have discovered that arsenic exposure is strongly correlated with increased risks of cardiovascular ailments, carotid atherosclerosis [49], ischemic heart disease and mortality due to vascular disease [50]. The distinct association with manifestations of generalized arteriosclerosis supplies certainty on causality. However, the underlying approaches have not been well-defined. Large-scale prospective studies that have been using pertinent biomarkers can help in identifying pathways by which arsenic develops and stimulates vascular disease [51]. According to several studies, it has been revealed that arsenic present in drinking water can develop cardiovascular diseases, especially in Taiwan [49,52,53]. In China and Bangladesh, it was reported that electrocardiogram changes in exposed populations can result in escalating risk of arrhythmia, mortality, cerebrovascular and cardiovascular disease [47,54].

Evidence related to increased disease risks caused by arsenic methylation: Arsenic can cause health ramifications that differ from one individual to another. In addition, it must be understood that several factors are involved such as genetics, age of exposure, diet and smoking habits that can influence the extent of seriousness of the health diseases. Past research studies have discovered that arsenic metabolism differs among individuals and this can cause significant differences in the severity of health diseases generating from arsenic metabolism. The main method that facilitates inorganic form of arsenic metabolism in human bodies is methylation [55]. As the Arsenic enters the body, the methylation process starts that methylates InAs to monomethylarsonic acid (MMA5), which transforms into monomethylarsonous acid (MMA3). MMA3 takes shape of dimethylarsinic acid (DMA5) that consequently turns into dimethylarsinous acid (DMA3).

It must be understood that in human bodies, this process remains incomplete, thereby arsenic remaining as InAs and MMA. In the case of humans, arsenic elimination takes place through urinary excretion, and internal metabolism is reflected through the various components of InAs, DMA and MMA in urine [56,57]. The portion of MMA, InAs and DMA found in human urine are usually utilized as biomarkers of the extent to which humans are involved in methylating absorbed InAs. Absorbed InAs involves around 10% to 15% MMA, 10% to 20% InAs and 60% to 75% DMA, although there are abundant situations in which there is a large differences in individuals' ingested InAs [58]. A significant pathway used for facilitating detoxification is called as methylation of InAs. The reason is that the methylated enzymes that are frequently gauged in urine samples-DMA and MMA are more frequently excreted and considered as less toxic in nature as compared to InAs [59,60].

DMA3 and MMA3 are unbalanced in human urine and hence have been gauged in few research studies related to mechanisms of human body. However, it must be taken into consideration that MMA3 contains an increased poisonous content *in vitro* as compared to its pentavalent type. In addition, MMA3 is considered as even more poisonous than trivalent InAs [61,62]. From these results, it can be stated that MMA3 can be the most poisonous specie of absorbed arsenic.

Presence of arsenic - resulting in genotoxicity, oxidative stress and DNA disruption: Many experimental observations determine that genotoxicity caused by arsenic refers to the process of generating ROS during the biotransformation phase of arsenic. When ROS are produced, it can facilitate DNA adducts; this can break DNA strand, thereby causing chromosomal abnormality [63]. Arsenic act as an impediment on individual's health and can cause serious ailments such as oxidative stress, genotoxicity and ineffective DNA repair capacity. Numerous research studies conducted in Latin America have proved that abnormality in chromosomes were more ubiquitous in Mexican people due to high arsenic exposure (As: 0.39 mg/L) than those with low arsenic exposure (0.019–0.026 mg/L) [64]. Likewise, a significant increase ($P<0.001$) in sister chromatid exchange was detected in Argentina's population where arsenic content in drinking water was 0.13 mg/L [65]. The studies conducted in Chile revealed that arsenic emerging by evaluating micronucleus induction from occupational and environmental exposure could result in genotoxic effects [66,67]. Prevalence of As significantly damaged DNA and this resulted in increased level of tumor suppressor protein p53 for individuals who were highly exposed to vulnerable arsenic content [68-70]. It was observed in Mexico that improving any genotoxicity of as would have adverse effects on DNA repair competencies.

Conclusions

It can be epitomized that the numerous individuals in Asia are subject to the damaging arsenic toxification and related diseases that can cause mortality. It is recommended that researches related to minimize and mitigate arsenic in most affected places must be conducted in future. This will improve public health. Moreover, findings resulting from future genetic epidemiologic and molecular studies can help in determining the potential implications for preventing and curing arsenic-related toxicities across the world.

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