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Review Paper

Speciation and Toxicity of Arsenic : A Human Carcinogen

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Abstract

Arsenic is an element found in nature in rocks, soils, water and air in fact, it is one of the most common elements on earth. Arsenic is widely distributed throughout Earth's crust, generally as arsenic sulfide or as metal arsenates and arsenites. The major source of arsenic pollution in the environment is the smelting of ores such as those of gold, silver, copper and others. Arsenic from these sources is distributed in the air, water, soil and finds its way into the human system by way of direct inhalation or through contamination of food and consumer products. The world health organisation (WHO) recommended that many authorities reduce their regulatory limits and it has established a provisional guideline value of 10 µg/l for arsenic in drinking water. While arsenic has been used historically in industry in fertilizers and preservatives, it is probably best known as a poison, toxic to humans who ingest it. Large doses are fatal relatively quickly, while smaller doses over time can cause diseases such as several types of cancer and skin disorders. Arsenic can become an environmental hazard when it is weathered from local geologic units and enters the groundwater supply. In the world today, many populations are at risk for arsenic poisoning due to exposure from contaminated drinking water. Arsenic contamination of drinking water is presently a worldwide epidemic. Contaminated drinking water has been found in Argentina, Chile, Mexico, China, Hungary, West Bengal, Bangladesh and Vietnam. Of these regions, West Bengal and Bangladesh are most seriously affected in terms of the size of the population at risk and the magnitude of the health problems. An estimated 300,000 people in West Bengal alone suffer from arsenic-induced skin lesions. Serious illnesses related to arsenic such as melanosis, keratosis, cancer, and gangrene have been reported in West Bengal and Bangladesh. In the process of arsenic metabolism, inorganic arsenic is methylated to monomethylarsonic acid and finally to dimethylarsinic acid, followed by excretion through urine. Thus, arsenic exposure may cause DNA hypomethylation due to continuous methyl depletion, facilitating aberrant gene expression that results in carcinogenesis. Further, though arsenic is nonmutagenic, it interacts synergistically with genotoxic agents in the production of mutations, and also induces chromosome abnormalities and cell proliferation.

Keywords: Arsenic, pollution, drinking water, contamination, toxic.

Introduction

Arsenic, a metalloid, occurs naturally, being the twentieth most abundant element in earth's crust and is a component of more than 245 minerals. The inorganic forms consisting mostly of arsenite and arsenate compounds are toxic to human health. Humans are exposed to arsenic primarily from air, food and water. Drinking water may be contaminated with arsenic from arsenical pesticide, natural mineral deposits or improperly disposed arsenical chemicals. However, elevated arsenic level in drinking water is the major cause of arsenic toxicity in the world. Reports of arsenic contamination in water are available from more than 30 countries in the world[1]. However, the major regions affected are in the river basin of the Ganga, Brahmaputra and Meghna in India and Bangladesh with an estimated 25 million people in Bangladesh and 6 million people in West Bengal, India exposed to arsenic contaminated ground water[1]. In India, though cases of arsenic toxicity including liver fibrosis due to drinking of arsenic contaminated water were reported from Chandigarh in early 1978[2], occurrence of large number of cases of arsenic induced skin lesions were reported from Kolkata, West Bengal in 1984[3]. Since then incidences of chronic arsenic toxicity have been reported in the most States adjoining the upper, middle and lower Ganga and Brahmaputra plain. Arsenic contamination has been found in the States of Bihar, Uttar Pradesh, Jharkhand, Assam, Chhattisgarh and Andhra Pradesh[4, 5].

Most of arsenic problems in third-world countries today are caused by natural erosion. One important mechanism through which the groundwater is polluted with arsenic is the reduction of iron oxyhydroxide (FeOOH) by bacteria and subsequent desorption of arsenic from the iron surfaces. In the Bengal Basin (part of Bangladesh and West Bengal), it is the main mechanism by which ground waters become contaminated with arsenic[6]. That does not mean humans are exempted from blame for the present arsenic crisis; significant arsenic pollution has occurred through the use of pesticides, herbicides, crop desiccants and additives to animal feed[7].

Over the past two or three decades, occurrence of high concentrations of arsenic in drinking-water has been recognized as a major public-health concern in several parts of the world.

There have been a few review works covering the arsenic-contamination scenario around the world[8-10]. With the discovery of newer sites in the recent past, the arsenic-contamination scenario around the world, especially in Asian countries, has changed considerably. Before 2000, there were five major incidents of arsenic contamination in groundwater in Asian countries: Bangladesh, West Bengal, India, and sites in China. Between 2000 and 2005, arsenic-related groundwater problems have emerged in different Asian countries, including new sites in China, Mongolia, Nepal, Cambodia, Myanmar, Afghanistan, DPR Korea, and Pakistan. There are reports of arsenic contamination from Kurdistan province of Western Iran and Viet Nam where several million people may have a considerable risk of chronic arsenic poisoning. The summary of the current global scenario of arsenic contamination is shown in figure-1.

Sources of different forms of arsenic: The principal natural reservoirs of arsenic are rocks. Release and mobilization of arsenic from these sources constitute the availability of this element in soil, water and air in various forms. As a result, arsenic is ubiquitous in our environment, and humans are always and unavoidably exposed to this toxic metalloid. Under normal ecological conditions, the level of arsenic bioavailability is not a threat for human health. Soils may contain arsenic levels between 0.1 and 40 ppm[11-12], if the underlying bedrock is not disturbed or redistributed by natural or pedogenic processes[11]. A large number of man-made arsenic compounds were used in agriculture as effective agents against pests, parasites or weeds and they gradually accumulated in the soil[11-13.] Further, concentrations of arsenic in the environment may be elevated due to certain other anthropological activities resulting in significant increase in the human exposure to arsenic[11-14] (figure 2). The solubility, stability and cellular toxicity of various forms of arsenic are widely different. Thus, studies in the chemical form of arsenic especially the two inorganic arsenic species, arsenate (As^{5+}) and arsenite (As^{3+}), their transformation, persistence and bioavailability are pertinent in the understanding of levels of human exposure to arsenic. Chemistry of inorganic arsenic in aquatic environment, especially with variable pH and oxygen availability, is unusually complex. The important feature is that in highly aerated condition arsenate salts are dissociated in all four arsenic acid (As^{5+}) species, H_3AsO_4, $H_2AsO_4^{1-}$, $HAsO_4^{2-}$ and AsO_4^{3-}. However, in mild reducing condition, arsenous (As^{3+}) acid species, H_3AsO_3, $H_2AsO_3^{1-}$ and $HAsO_3^{2-}$ may be stable. Arsenic acid (As^{5+}) is the least toxic of the inorganic forms and arsenous acid (As^{3+}) is more toxic *in vivo* than arsenic acid and also inhibitorier *in vitro*. A large number of diverse chemical and biological reactions, viz. oxidation, reduction, adsorption, precipitation, methylation and volatilization participate actively in the cycling of this toxic element (Figure 3). These reactions control the availability of arsenic, and hence, arsenic concentrations effectively exposed to humans are governed more by arsenic speciation than by the total amount of arsenic.

Arsenic Chemistry-Arsenic forms and mobility: Arsenic rarely occurs in a free state, it is largely found in combination with sulphur, oxygen, and iron[15-16]. In groundwater, arsenic combines with oxygen to form inorganic pentavalent arsenate and trivalent arsenite. Unlike other heavy metalloids and oxyanion-forming elements, arsenic can be mobilized at the pH values typically found in surface and groundwaters (pH 6.5 to 8.5) and under both oxidizing and reducing conditions[17]. While all other oxyanion-forming elements are found within the µg/L range, arsenic can be found within the mg/L range. Arsenic can occur in the environment in several oxidation states (−3, 0, +3 and +5), often as sulfides or metal arsenides or arsenates[18]. In natural water its predominant forms are inorganic oxy-anions of trivalent arsenite (As(III)) or pentavalent arsenate (As(V). It usually occurs in natural waters at concentrations of less than 1 or 2 µg L– 1. However, in natural groundwater reservoirs where there are sulfide mineral deposits and sedimentary deposits derived from volcanic rocks, the concentrations can be significantly increased (up to 12 mg L–1). The toxicity of different arsenic species varies in the order arsenite > arsenate > monomethylarsonate > dimethylarsinate. Trivalent arsenic is about 60 times more toxic than arsenic in the oxidized pentavalent state, and inorganic arsenic compounds are about 100 times more toxic than organic arsenic compounds[16]. The organic forms of arsenic are quantitatively insignificant and are found mostly in surface waters or in areas severely affected by industrial pollution. Increased risks of arsenic related diseases have been reported to be associated with ingestion of drinking-water at concentrations of < 50 µg L– 1[18]. The relative concentrations of As (III) to As(V) vary widely, depending on the redox conditions in the geological environment[16].

Arsenic speciation: Redox potential (Eh) and pH are the most important factors controlling speciation of arsenic (and, to some extent, solubility) (figure 4). Under oxidizing conditions at pH less than 6.9, $H_2AsO_4^-$ is the dominant species, whilst at higher pH, $HAsO_4^{2-}$ becomes dominant. Under reducing conditions at pH less than 9.2, the uncharged arsenite species H_3AsO_3 is dominant. In contrast to the pH dependency of As(V), As(III) was found virtually independent of pH in the absence of other specifically adsorbed anions[9]. Most often, more trivalent arsenic is found in reducing groundwater conditions than pentavalent arsenic, whereas the converse is true in oxidizing groundwater conditions. The stabilities of arsenic species under different pH and redox conditions are shown in table 1 and the dissociation reactions and corresponding equilibrium constants of H_3AsO_4 and H_3AsO_3 are shown in table 2[19]. Figures 5a and b show the distribution of As(V) and As(III), as a function of pH, respectively. As(III) exists as non-dissociated at neutral and slightly acidic conditions and only at pH > 8 considerable amount of anionic species are found. As(V), on the other hand, is almost completely dissociated and present in the form of monovalent, divalent and trivalent anions[20]. In practice, most studies in the literature report speciation data without consideration of the degree of protonation.

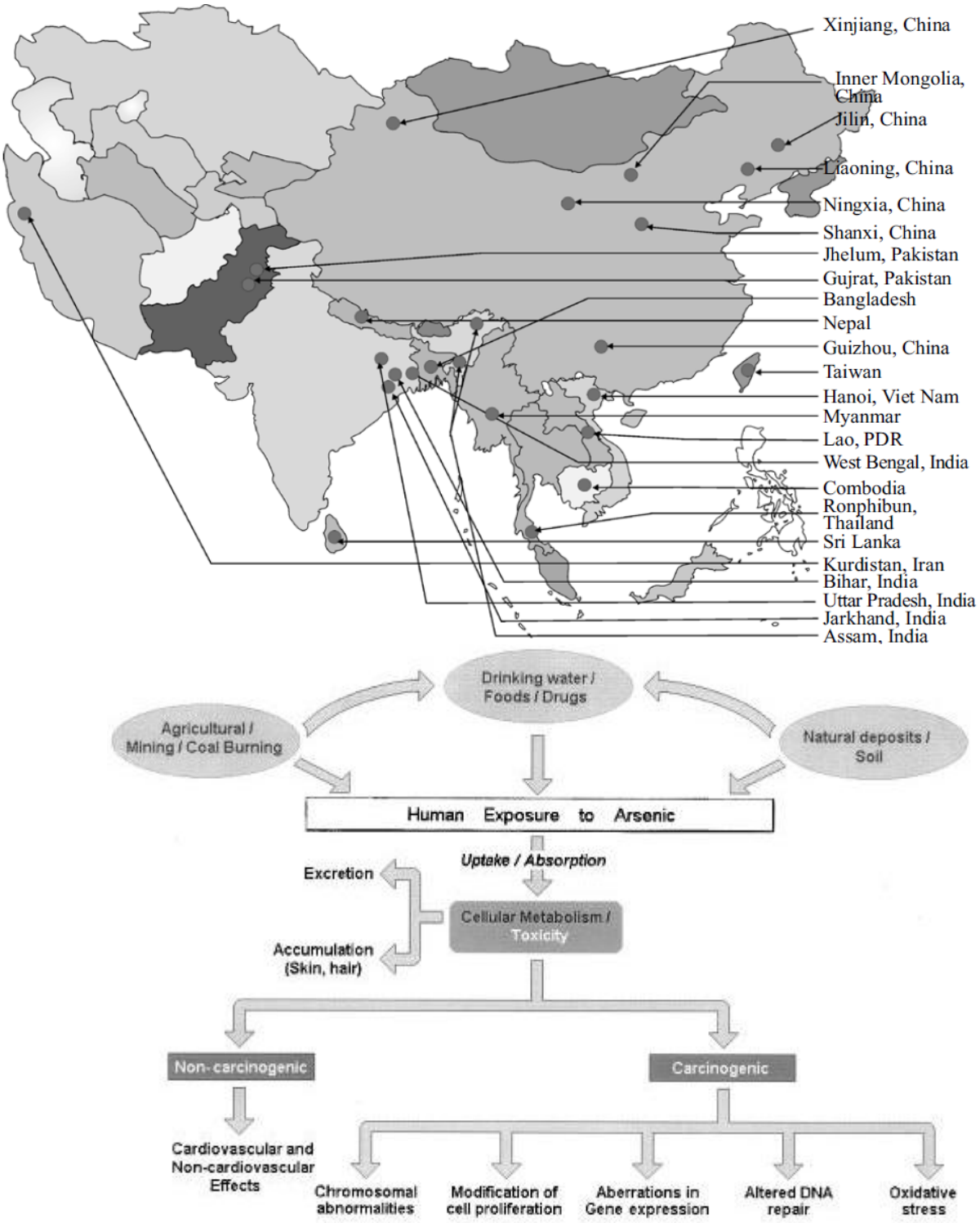

Figure-2
Sources of human exposure to arsenic and various modes of arsenic toxicity

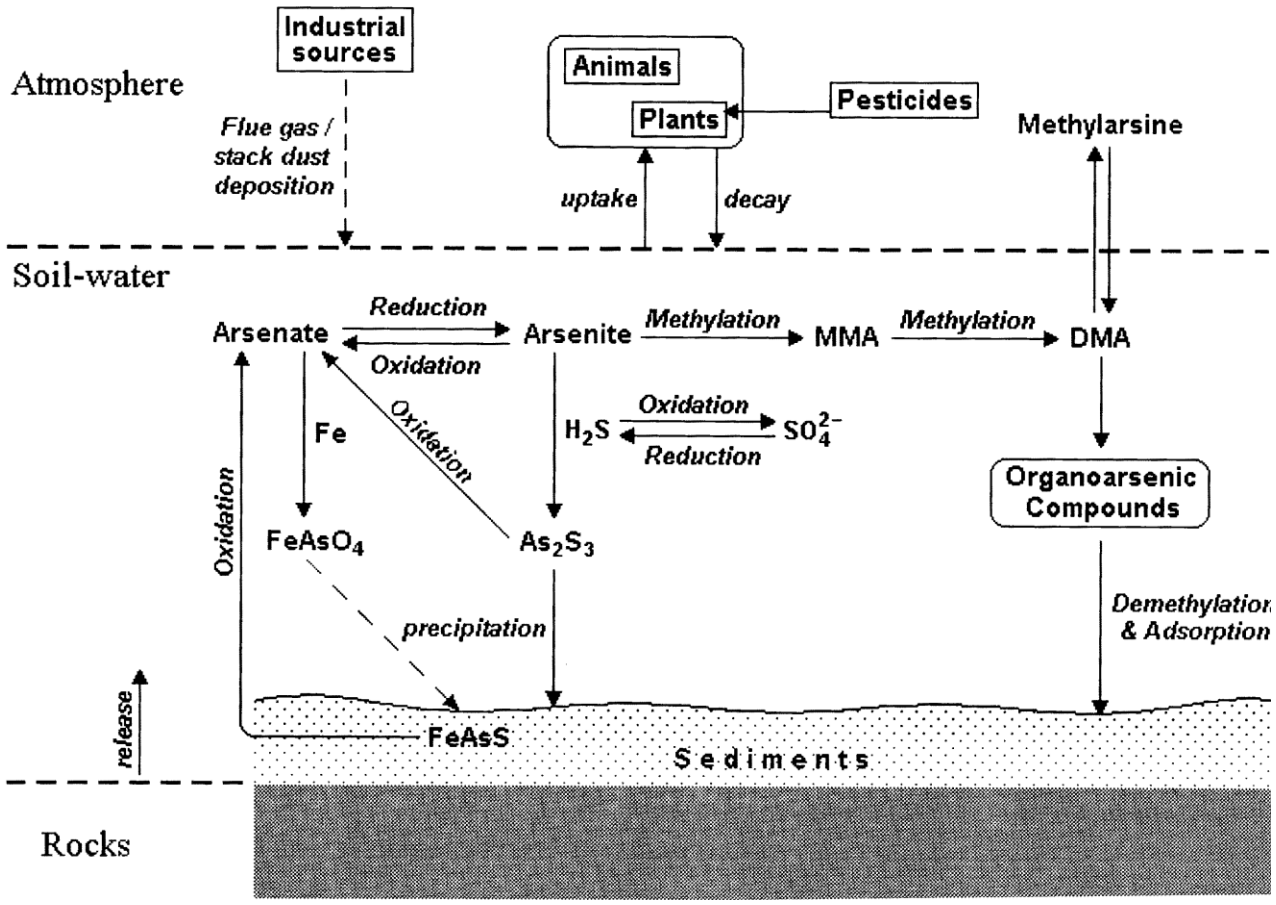

Figure-3

Arsenic cycle in the environment[27]. Major reactions in the soil–water and sediment–rock systems to influence the environmental transport, distribution and availability of arsenic. Oxygen availability controls the arsenate–arsenite redox reactions. Adsorption and precipitation of arsenate and arsenite immobilize the soluble arsenic. Slow release of arsenic from rocks and sediments or oxidative dissolution of arsenopyrite (FeAsS) from sediments contribute flux of arsenic in the environment. Methylation of arsenite to monomethylarsonic acid (MMA) or dimethylarsinic acid (DMA) followed by other organoarsenic compounds, constitute the major biological reactions in the arsenic cycle[11, 14]

Table-1
Stability of Arsenic Species

Reducing Conditions		Oxidizing Conditions	
pH	**As (III)**	**pH**	**As(V)**
0-9	H_3AsO_3	0-2	H_3AsO_4
10-12	$H_2AsO_3^-$	3-6	$H_2AsO_4^-$
13	$HAsO_3^{2-}$	7-11	$HAsO_4^{2-}$
14	AsO_3^{3-}	12-14	AsO_4^{3-}

In the presence of extremely high concentrations of reduced sulphur, dissolved arsenic-sulphide species can be significant. Reducing, acidic conditions favour precipitation of orpiment (As_2S_3), realgar (AsS) or other sulphide minerals containing coprecipitated arsenic. Therefore high arsenic waters are not expected where there is a high concentration of free sulphide. Thioarsenite species will be more important at neutral and alkaline pH in the presence of very high sulphide concentrations.

Table-2
Dissociation constants of Arsenate and Arsenite

Speciation	Dissociation reactions			pKa
Arsenate As(V)	H_3AsO_4	⇌	$H^+ + H_2AsO_4^-$	2.24
	$H_2AsO_4^-$	⇌	$H^+ + HAsO_4^{2-}$	6.69
	$HAsO_4^{2-}$	⇌	$H^+ + AsO_4^{3-}$	11.5
Arsenite As(III)	H_3AsO_3	⇌	$H^+ + H_2AsO_3^-$	9.2
	$H_2AsO_3^-$	⇌	$H^+ + HAsO_3^{2-}$	12.1
	$HAsO_3^{2-}$	⇌	$H^+ + AsO_3^{3-}$	13.4

Exposure due to industrial activities: Arsenic present in various metal ores or coal is released during the smelting process or in coal burning, which produces stack dust and flue gas to contaminate the soil and water with arsenic, downwind from the operation[21] (figure 3). As a result arsenic pollution in mining places and in smelting or coal-burning in thermal power plants continues to be a severe health problem. The environmental survey with the epidemiological study,

conducted between 1987 and 1994 in the southern part of Thailand where mining was the primary resource, recorded prevalence of chronic arsenic poisoning in the population of the affected districts of Thailand[22]. In Kolkata, a factory that was manufacturing the pesticide, Paris green (K-acetoarsenite), contaminated the subsurface and even the underground aquifer surrounding the factory affecting several thousand people of the region. A clinical investigation[22] of 20 patients from this place revealed significant prevalence of keratosis, liver damage and respiratory disease. The study also noted that metabolism of arsenic in the body after its ingestion, and its clearance were quite variable in man and no effective treatment protocol was available for the amelioration of chronic arsenic toxicity. Similarly, in the vicinity of a lead factory at Kolkata, the soil and surface water were found highly contaminated not only with lead but also with several other toxic metals, including arsenic. All these reports suggest that effective environmental safety measures should be innovated by the industry.

Arsenic pollution in drinking water: The arsenic calamity reported from many parts of the world[23] is thought to be due to contamination of underground water and of geogenic origin. The first two epidemiological studies of arsenic-induced dermatoses from consuming arsenic-contaminated water were conducted by Tseng and Saha in Taiwan and West Bengal (India), respectively. Subsequently, Saha made an extensive survey during the period of 1983–1987 from 61 villages of 7 districts of West Bengal (WB). He had detected 1214 cases of chronic arsenical dermatoses (melanosis and keratosis), having skin cancer in 6 cases. Saha also noted that all the affected individuals were villagers of poor economic status (mostly agricultural labourers) who were exposed to low doses of arsenic for several years. This report was further substantiated by other workers indicating that about two lakh people (more than 0.6% of total population) in the arsenic-endemic regions of WB have arsenical skin lesions, and one million people are at risk due to consumption of water having arsenic concentrations 10 to 20-fold higher than the maximum permissible limit of 0.05 ppm. The source of arsenic resulting in pollution of aquifer in this vast region of WB is thought to be geogenic. It is suspected that arsenopyrite-rich sediment is being slowly solubilized, because of increased oxygen availability due to the extensive removal of groundwater through shallow or deep tube-well used for irrigation[24]. From the hydrogeological point of view, a younger deltaic deposit brought by the river Ganga and sedimented at the right side of the river, is the source of arsenic in this region that spans a vast area of WB and the neighbouring country of Bangladesh. In a recent survey report, conducted jointly by School of Environmental Studies, (Kolkata) and Dhaka Community Hospital, Dhaka (Bangladesh), the investigators claimed that arsenic calamity in Bangladesh is more severe than in WB and fifty million people within thirty-four districts of Bangladesh would be at risk, in the absence of a proper 'watershed management'.

Arsenic–A human carcinogen: Arsenic toxicity and its potentiality in the development of cancer were known for a very long time, but carcinogenicity could not be directly tested because arsenic is yet to be shown to cause cancer in rodents. The reasons for these apparent interspecies differences are not known but may be related to distinct detoxification mechanisms or capabilities between humans and rodents. Consequently, the precise cellular mechanism of arsenic-induced carcinogenesis (arsenicosis) is not yet uncovered, though, in a large number of recent publications and in several international conferences held in different parts of the world, we find widespread interest regarding arsenic exposure and human health. Predominant manifestation of chronic arsenic toxicity is skin lesions characterized by pigmentation and keratosis (figure 6). However it produces protean systemic manifestation over and above skin lesions, important ones being chronic lung disease like chronic bronchitis, chronic obstructive pulmonary disease and bronchiectasis, liver disease like non cirrhotic portal fibrosis and other diseases like polyneuropathy, peripheral vascular disease, hypertension and ischeamic heart disease, diabetes mellitus, non-pitting edema of feet/ hands, weakness and anemia. Cancer of skin, lung and urinary bladder are important cancers associated with chronic arsenic toxicity.

Arsenic poisoning or intoxication from therapeutic use: Arsenic is known and used since the history of human civilization due to its highly toxic properties. Until recently different arsenic compounds such as potassium arsenite, arsenic iodide or arsenic trichloride were used, as medication for a variety of illness[25-26]. Before the 'preantibiotic era', the discovery of salvarson (arsphenamine) made it the main medicine used against syphilis. Generally uses of these drugs have been largely discontinued because of high toxicity of arsenic compounds. Nevertheless, several organic compounds or herbal products containing arsenic are still in use in human medicine. Tryparsamide ([4-[2-amino-2 oxoethyl]-amino]-phenyl] arsonic acid[25]) is used to treat African sleeping sickness, a disease caused by parasitic protozoa of the *Trypanosoma brucei* subgroup. Retinoic acid (RA) is a potent antileukaemic drug used in acute promyelocytic leukaemia (APL) patients. Arsenic trioxide can also induce complete remission in APL patients. However, arsenic trioxide triggers rapid degradation of PML-RA receptor protein chimera (a fusion product of PML and RA receptor protein gene) from both RA-sensitive and RA-resistant APL patient. Understanding the molecular basis of differences in the effects of arsenic trioxide and RA may guide the clinical use of arsenic compounds and could be effectively introduced into the management of leukaemia that does not respond to RA. In fact, arsenite was shown to induce apoptosis in different leukaemia cell lines. Thus, arsenic is used in the Ayurvedic system of medicine in India to control blood counts of patients with haematological malignancies.

Conclusion

Arsenic, a metalloid, ranked first in a list of 20 hazardous substances by the Agency for Toxic Substances and Disease Registry and United States Environmental Protection Agency.

The evidence for carcinogenicity of arsenic is very strong in humans, but weak in animals, a unique and different scenario than is found for other carcinogens. At present there are no recognized models for the study of arsenic-induced carcinogenesis. It is non-mutagenic in bacterial or human cells, though it interacts synergistically with genotoxic agents in the production of mutations. However, it is convincingly established that arsenicosis is mediated through chromosome abnormalities, modification of gene expression, and cell proliferation due to oxidative stress and other uncharacterized or poorly defined physiological modifications or aberrations. Exposures to arsenic large enough to cause acute toxic effects would be easily recognized and the source of exposure would be found and eliminated. But the problem lies in the fact that low doses of arsenic that would be too low to cause overt acute toxicity, finally be recognized after a long time with the development of cancer. This has demanded a serious effort to trace all the possible sources that cause human exposure of this 'king of poison'. Finally, it is worth mentioning that arsenic poisoning in humans should not be considered a natural phenomenon, rather it is due to wrong policy of uncontrolled industrialization and ignorance to develop an effective water management of surface-water resource.

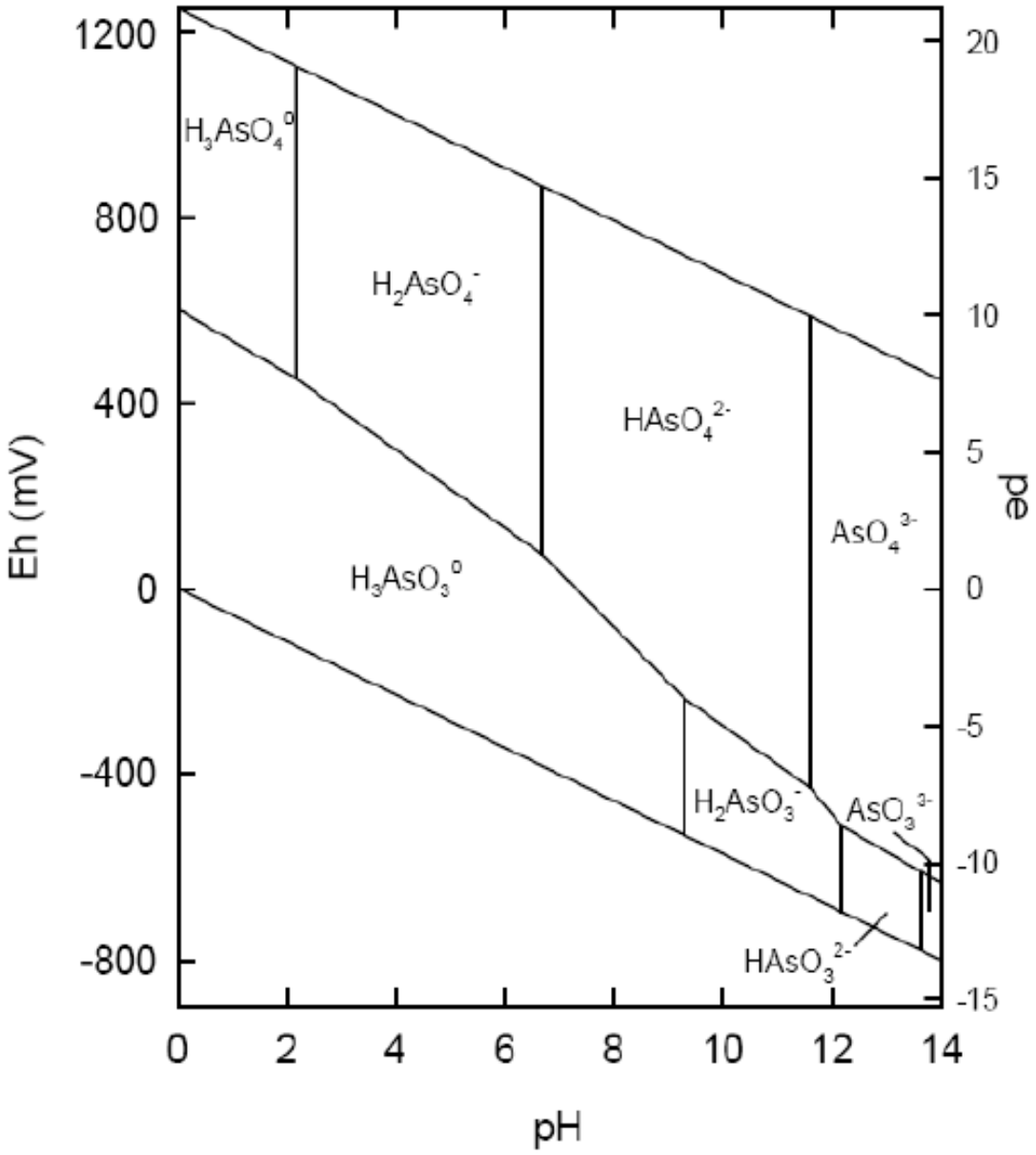

Figure-4
Eh/pe-pH diagram for Arsenic

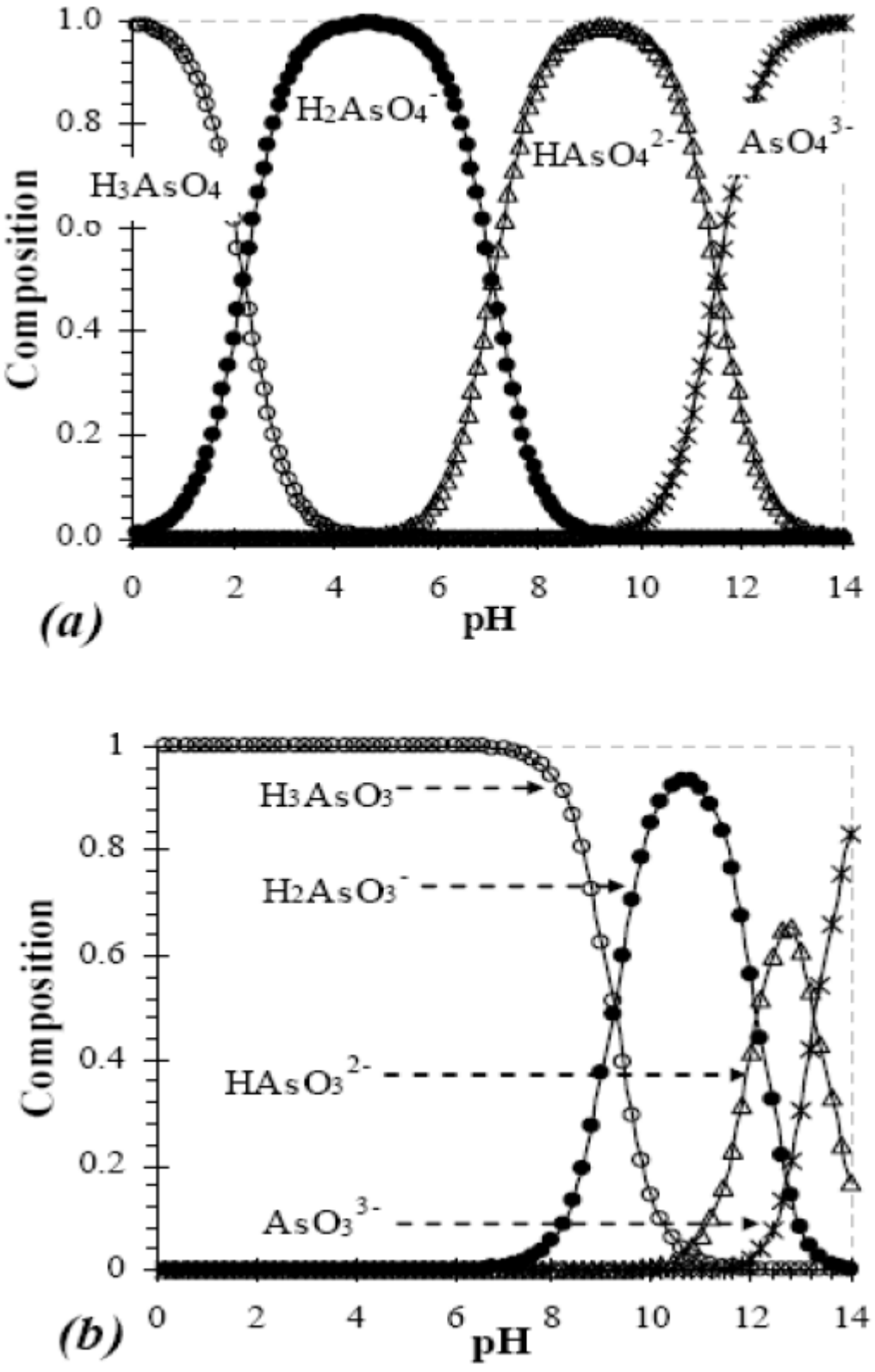

Figure-5
Distribution of arsenate (a) and arsenite (b) as a function of pH

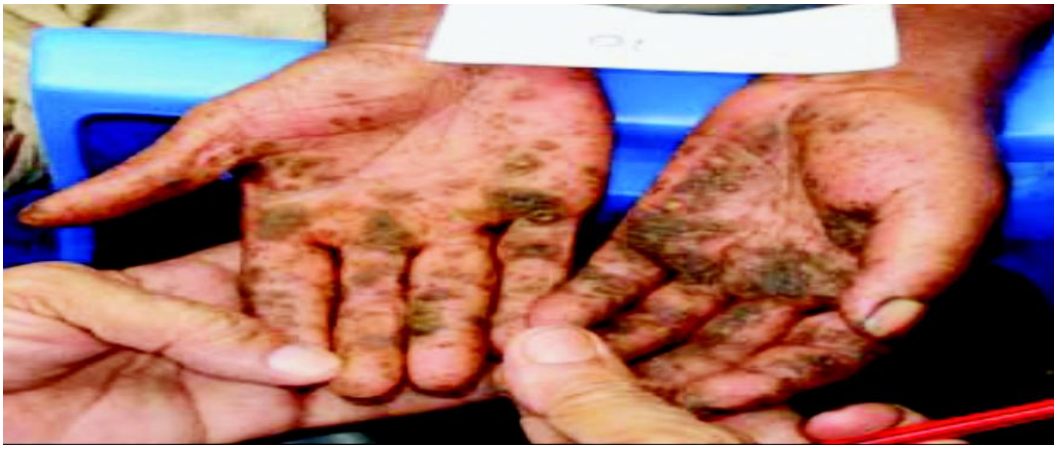

Figure-6
Arsenical keratosis (nodular and confluent thickening) affecting both palm

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