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ARSENIC: IT'S TOXICITY AND IMPACT ON HUMAN HEALTH

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Abstract: Water pollution is a major problem in modern life. Almost all the heavy metals are toxic at higher concentrations and some are lethalat very low concentration. Arsenic is a naturally occurring element present in water, food and soil, but now-a-days this element is one of the rapidly emerging serious environmental pollutants; released into the environment through industrial and agricultural usage. In many parts of India, the ground water is contaminated with arsenic. The genesis of arsenic pollution is not understood fully, yet it is thought that natural geological weathering is mostly responsible for the dissolved arsenic in ground water. Arsenic exposure to human causes degenerative, inflammatory and neoplastic changes in skin, respiratory system, blood, lymphatic system, nervous system and reproductive system. There is no particular remedial action for chronic arsenic poisoning. Nearly 100 million people are to be affected by arsenic diseases like spots on the skin, high blood pressure, diabetes, skin cancer, cancer of urinary bladder, kidney and lungs. Low socio-economic status and malnutrition may increase the risk of chronic toxicity. There is a strong relationship between chronic ingestion of arsenic and deleterious human health effects. 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. In this review article, authors tried to provide an overview of some of the major effects documented in the scientific literature.

Keywords: Arsenic, Human health, India, Prevention, Toxicity.

INTRODUCTION

Out of the total available fresh water, ground water is the main source of drinking water in our country. Industrialization and change in life style have incorporated lot of unwanted chemicals in ground water, which shows toxicity and annihilate the normal functioning of biological molecules (Prakash, 2017). Urbanization, domestic sewage and tremendous increase in population also create the huge problem of pure drinking water in the developing countries including India. Contamination of arsenic in ground water is the global problem and millions of people are at a risk of arsenicosis (Maharajan *et al.,* 2005). The catastrophe of arsenic toxicity, caused by arsenic contaminated water, has already been reported in many countries of the world, namely in Bangladesh, India, Nepal, Cambodia, Myanmar, Taiwan, Mongolia, Vietnam, China, Afghanistan, Pakistan,

Argentina, Mexico, Chile and the United States (Mukherjee *et al.,* 2006).

The arsenic is released by reductive dissolution of iron oxyhydroxides (Acharyya *et al*., 1999). It is classified as metalloid (semi metallic in nature), having intermediate chemical properties between typical metals and non-metals. Thus, arsenic is capable of forming alloys with metals, but it also readily forms covalent bonds with carbon, hydrogen and oxygen (Prakash and Verma, 2020a). It is a widespread environmental contaminant and released into the environment through both geogenic processes as well as anthropogenic activities such as metal smelting and chemical manufacturing (Prakash and Verma, 2019a). It is considered to be a toxic trace element, and ecological dangers can arise if large amounts of arsenic are released into the environment as a result of industrial and agricultural activities. Increased concentrations of arsenic in ground water have been reported from several countries, including India (Verma and Prakash, 2019a).

Arsenic forms numerous inorganic and organic compounds because it possesses several different valence (*i.e*.-3,-1,0,+3, and +5) or oxidation states, which results in the changes in different biologic behavior of its compound (Verma and Prakash, 2019b). In natural water, arsenic is present in both inorganic and organic forms but the inorganic form has been found to be more toxic (Verma and Prakash, 2020a). The trivalent salt of arsenic (sodium arsenite) is more toxic than other forms (Prakash and Verma, 2020b).The most common source of elevated arsenic concentrations in the environment is attributed to anthropogenic activities. Mining activities have contributed to the contamination of soil and water primarily. However, other anthropogenic activities using arsenic, such as agriculture, forestry, and industry, have also contaminated soil and water at a localized scale (Smith *et al*., 2003).

More than one hundred million people are at high risk of elevated arsenic exposure, mainly via drinking water, as well as by industrial emissions (Prakash and Verma, 2020c). Inorganic arsenic of geological origin is found in ground water used as drinking water in several parts of the world (Verma and Prakash, 2020b). High concentration of arsenic in groundwater in the north-eastern states of India has become a major cause of concern (Prakash and Verma, 2020d).The presence of arsenic in drinking water causes toxic and carcinogenic effects on human beings. It is the first metalloid to be identified as a human carcinogen and most cases of chronic arsenicosis are associated with continual intake of arsenic-contaminated water (Prakash and Verma, 2020e).

Arsenic affects the human populations regardless of sex and age but the children are less susceptible to arsenicism (Chowdhury *et al*., 2003). Chronic ingestion of inorganic arsenic causes multisystem adverse health. High dose of arsenic in drinking water or arsenic contaminated water is very harmful and causes gastro-intestinal disorders including liver and pancreas, cardiovascular diseases, renal diseases, skin diseases and nerve tissue injuries, chronic lung disease, reproductive disorder and cancer of skin, liver, lungs, kidney and urinary bladder (Xu *et al.,* 1991; Wang *et al*., 2003; Anawar *et al*., 2003). Arsenic contaminated drinking water is also responsible for spontaneous abortion, stillbirth and infant mortality (Aschengrau *et al*., 1989; Hopenhayn-Rich *et al*., 2000).

Arsenic containing pesticides are not only harmful to human health but are also harmful to all aquatic life including fishes (Prakash and Verma, 2019b). Consumption of the arsenic through contaminated fishes collected from the polluted waters might also contribute to bioaccumulation of arsenic in human beings. They are however, endangered by diet-borne pollutants transferred along the food chain (Das *et al.,* 2012).

Permissible limit of Arsenic: 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 (EPA, 2001) and the guideline value for concentration of arsenic in drinking water is recommended by the WHO is also 10 µg/l (WHO, 2001). Drinking water with MCL (10 µg/l) or below to MCL is not hazardous to the population. The

standard of most developing countries is 50 µg/l, which is several times higher than the MCL and more hazardous to the population. The maximum permissible limit of arsenic in India is set to be 0.05 ppm, while according to guidelines of WHO it is 0.01ppm, but in many arsenic affected area of India, its concentration was more than 0.2 ppm in well and underground water, which is used as the source of drinking water. 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). It was reported that the concentration of arsenic in water was ranged from 50-1354 mg/ L and prevalence of skin lesion was 44.80%. It is necessary to reset the standard in these countries.

ROUTE OF ARSENIC ENTRY IN HUMAN BODY: 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, arsenic containing drugs are used to treat some diseases like syphilis, asthma, rheumatism, cough, pruritus, itching, trypanosomias is and acute promyelocytic leukemia (Ko, 1999; Wang *et al.*, 2003). Sea food with elevated concentration of organic arsenic is also one of the main sources of arsenic poisoning in human (ATSDR, 2006).

METABOLISM OF ARSENIC IN HUMAN: Most ingested and inhaled arsenic is well absorbed through the gastrointestinal tract and lung into the blood stream. An affect of inorganic arsenic in the form of airborne particle of arsenic trioxide on respiratory system mainly occurs in industrial area. In blood, 95 to 99 % of absorbed arsenic bound to the globin of hemoglobin and is then distributed in a various organs including the lungs, liver, kidney, and skin. Ingested arsenic has a shorter half-life than inhaled arsenic due to more rapid biotransformation in the liver. About 70% of the arsenic is excreted mainly through urine. The rate of decrease of arsenic in the skin appears to be especially low compared with the rate for other organs (Saha *et al.*, 1999).

Biotransformation of toxic inorganic arsenic into less toxic methylated arsenic mainly occurs in liver but other organs also have the arsenic methylation activity (Vahter, 2002). In this process inorganic arsenic is enzymatically bio transformed to methylated arsenicals including monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), which are the end metabolites and the biomarker of chronic arsenic exposure (Biggs *et al.*, 1997; Thomas *et al.*, 2001).

iAs (V) → iAs (lll) →MMA (V)
→MMA (lll)→DMA (V)

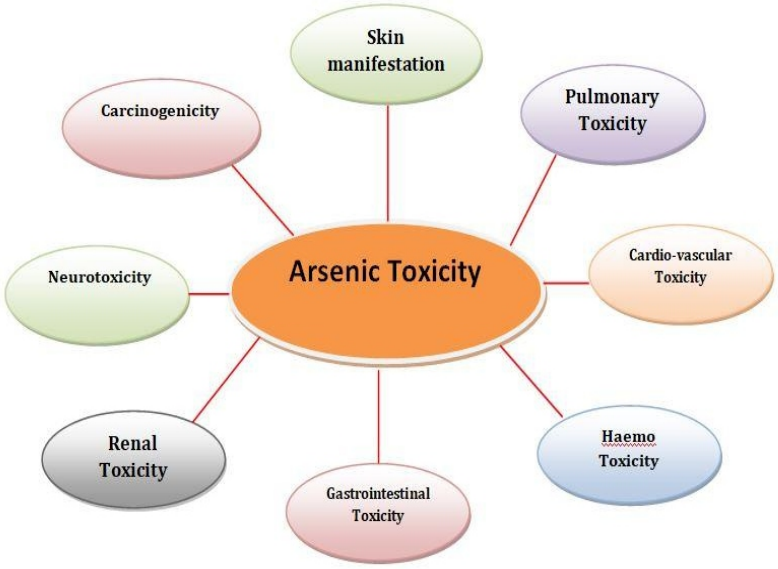
The activity of first methylation step is represented by the ratio of iAs/ MMA. Its high ratio indicates poor methylation and activity of second step is denoted by the ratio of MMA / DMA. Its low ratio indicates good methylation (Del Razo *et al.*, 1997; Vahter, 1999).The order of toxicity of arsenicals is:

MMA (lll) >Arsenite (lll) > Arsenate (V) >
MMA (V) = DMA (V).

In arsenic biotransformation, the intermediate product MMA is highly toxic than other arsenicals, which might be responsible for the arsenic-induced carcinogenesis and other effects (Styblo *et al.*, 2000; Singh *et al.*, 2007). Thus, the methylation of arsenic is considered to be an activation process, not a detoxification (Concha *et al.*, 1998). Deficiency of protein, folate and vitamin B in diet affected the biotrasformation of arsenic by which arsenic is not excreted from body and causes its adverse health effects (Singh *et al.*, 2007).

ARSENIC TOXICITY IN HUMAN: Symptoms of acute arsenic poisoning usually occur within half an hour of ingestion but may be delayed if arsenic is taken with the food. Early symptoms of arsenic

intoxication may be muscular pain, abdominal pain with nausea, vomiting and diarrhea, flushing of skin. Chronic ingestion of inorganic arsenic causes multi system adverse health effects including cancer of skin, lung, liver, kidney and urinary bladder (IARC, 1980). Increased exposure of arsenic is also associated with non insulin dependent diabetes mellitus (Rahman *et al.*, 1998; Wang *et al.*, 2003). The children with high arsenic in their hairs have less height than the children with low arsenic (Siripitayakunkit *et al.*, 2000b). Arsenic contaminated drinking water is also responsible for growth retardation, spontaneous abortion, stillbirth and infant mortality (Aschengrau *et al.,* 1989; Hopenhayn-Rich *et al.,* 2000).



Impact of Arsenic on Human Health

Skin manifestation: Chronic oral exposure to inorganic arsenic causes characteristic skin manifestation. It 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 (hyper-pigmentation), spotted melanosis (spotted pigmentation), non-melanoma (depigmentation) and leucomelanosis in which white and black spots are present side by side on the skin (Singh *et al.,* 2007). Melanosis is found mainly on the trunk and extremities or on the whole body (Mazumdar *et al.*, 1988). Characteristic rain drop pattern is the commonest cutaneous manifestation occurs as a result of hypopigmentation (Smith *et al.*, 2003). 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.*, 2003). Depigmentation an arsenic-induced skin lesions has the increasing risk of low-grade basal cell and squamous cell carcinoma and Bowen's disease, precancerous lesion (Abernathy *et al.*, 1999; Centeno *et al.*, 2000). The long-term ingestion of arsenic causes it 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).

Pulmonary Toxicity: The effect 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, trachea bronchitis and pulmonary insufficiency due to emphysematous lesions (WHO, 1981). Chronic

cough, bronchopulmonary disease, asthmatic bronchitis, asthma and high rate of chronic cough is a common complication of ground water arsenic toxicity (Saha, 1995).

Cardio-vascular Toxicity: Long term inhalation of inorganic arsenic could injure the blood vessels and causes cardio-vascular disease including arteriosclerosis (Zaldivar,1974).

Haemo Toxicity: Anaemia (decrease in RBC count and haemoglobin percentages due to haemolysis), thrombocytopenia (decrease in thrombocytes) and leucopenia (decrease in WBC count) are common symptoms in the persons inhabiting in arsenic prone areas (Mizuta *et al*., 1956) however, malnutrition is a major causes of anaemia in underdeveloped countries like India. The mechanism of hemolysis involved the depletion of intracellular GSH resulting in oxidation of sulfhydryl groups in the hemoglobin from ferrous to ferric in mice and rats (Saha *et al*., 1999). Arsenic damages the mitochondria and causes impaired mitochondrial functions, and accordingly might be expected to affect porphyrin metabolism (Saha *et al*., 1999).

Gastrointestinal Toxicity: The gastrointestinal toxicity damages the epithelial cells; resulting into gastrointestinal irritation that includes burning lips, painful swallowing, thirst, nausea and several abdominal colic (Environmental Protection Agency, EPA, 1984; Goebel *et al*., 1990). Sometimes severe acute gastrointestinal toxicity may cause death (Chakraborty and Saha, 1987). Arsenic alters the biochemical components of liver (Prakash and Verma, 2019a & 2020c; Verma and Prakash, 2019a & 2020a) hence it is required to drink quality water (Dwivedi, 2020).

Renal Toxicity: Like the liver, the kidneys will accumulate arsenic in the presence of repeated exposures. The kidneys are the major route of arsenic excretion, as well as major site of conversion of pentavalent arsenic into the more toxic and less soluble trivalent arsenic. Renal damage is secondary and occurs due to clogging of nephrons with hemolytic debris (Sittig, 1985). Arsine-induced hemolysis is likely to because tubular necrosis with partial or complete renal failure, requiring hemodialysis for removal of the hemoglobin bound arsenic (Fowler and Weissburg, 1974).

Neural Toxicity: Both the peripheral and central components of the nervous system can be damaged by arsenic (Schoolmeester and White, 1980). 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 was associated with cerebrovascular disease cerebral infarction (Chiou *et al.,* 1997)and peripheral neuropathy, which is similar to the Guillain-Barre syndrome (Goddard *et al*., 1992). Chronic arsenic exposure can lead to mental retardation and developmental disabilities such as physical, cognitive, psychological, and sensory as well as speech impairments (Brinkel *et al*., 2009). Arsenic exposure from drinking water was associated with visual perception in children but not the visual motor integration (Siripitayakunkit *et al*., 2000a) and reduced intellectual function in children (Concha *et al*., 1998). Besides these problems, arsenicosis diseases may cause psychological harms and affect mental health (Havenaar and van den Brink, 1997). The other effects of arsenic exposure are change in behaviors, confusion, disorientation, memory loss and cognitive impairment (Singh *et al*., 2007).

Carcinogenicity: Long-term effect of chronic expose to inorganic arsenic causes skin, lung, liver, kidney and urinary bladder cancer (IARC, 1980). 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 includes inhibition of DNA repair enzyme and DNA methylation, interference with tubulin dynamics and mitosis, induction of oxidative stress, and promotes cell clone immortalization (USEPA, 1997). The genotoxicity of inorganic arsenic includes both structural and numerical chromosomal abnormalities, increase in sister chromatid, gene amplification, and cell transformation (Warner *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 in the workers of manufacturing unit and to people, who worked in the industries of arsenic containing pesticides, chemical and metals smelting area.

PREVENTION: Prevention is better than cure. It is not possible to eliminate total arsenic and to afford the arsenic free drinking water to everyone, so authors recommend to use the alternative water source such as rainwater or to remove the arsenic from contaminated water. Balanced diet with pure quality water should be recommended to all people (Dwivedi, 2020; Mir *et al.*, 2020).

The most important remedial action for the person who suffered from arsenicosis, the first step is to prevent the use of arsenic contaminated drinking water to stop further exposure or providing the arsenic free drinking water or drinking water with arsenic below10 µg/l (Singh *et al.*, 2007).

The second step to educate the people regarding adverse effect of arsenic and aware the population to use the low arsenic water (below MCL) for drinking purpose and high arsenic water for other purposes that help to decrease the future exposure.

The most common antidote for arsenic and other metals poisoning is British anti-leusite (BAL),chemically 2,3-dimerceptopropanol but due to toxic activity BAL are less used as antidote. Presently thiolchelators like meso 2,3-dimercaptosuccinic acid (DMSA), sodium2, 3-dimercaptopropane-1-sulfonate (DMPS) and monoisoamyl DMSA (MiADMSA) are commonly used, both in acute and chronic arsenic toxicity (Domingo, 1995).

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 (Singh *et al.*, 2007).

CONCLUSION

This review provides an overview of the effects of arsenic on human health that explains arsenic pollution as a most important public health issue particularly in India. Chronic ingestion of inorganic arsenic causes multisystem adverse health effects. High dose of arsenic in drinking water causes skin disease, vascular disease, ischemic heart disease, renal disease, cardiovascular disease, lung disease, cerebro-vascular disease, neurological disorder, reproductive effects and cancer of skin, lungs, liver, kidney and bladder. Arsenic is very harmful toxic substance so preventive measure is essential to reduce its toxicity. Though there is recognition of the seriousness of the problem of arsenicosis among rural and urban population, but there is no effective treatment. All of us must be interested in increased preventive efforts not only because our population is at risk, but also because of the other conditions associated with the continued arsenic exposure in drinking water. Sensitization of community members and law enforcement authority to prevent separation and ostracism may be helpful to control arsenicosis. 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.

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