Arsenic Contamination and its Impact on the Environment

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Abstract
Arsenic (AS) toxicity is considered as one of the biggest environmental issue and a major public health problem. In this chapter we have summarized the impact of AS contamination on human health. A perusal of literature reveals that exposure to higher concentrations of AS is serious for a number of reasons. Such exposure for a longer period leads to ill effect on several organ systems of the human body. The adverse effects of inorganic AS cause many human diseases, human sufferings and increased human mortality and also affect various age groups variously. Population of some countries are more vulnerable to as contamination problems. Studies have revealed the mechanisms of many AS induced diseases particularly cancer, cardiovascular effects, immunological effects and neurological effects in human. This article presents the scientific information emerged especially during the last two decades in the field of the eco toxicological properties of AS and the potential mechanism of AS-induced toxicity, with a special emphasis on AS-induced carcinogenesis.

Introduction
Arsenic (AS) in high concentration is one of the dangerous toxicants for human health. Ground water and other heavy metals contamination are the main sources of AS pollution and have serious consequences on the human health and its effects, bio-accumulative nature, and persistence in the environment worsen the problem. In biological systems, heavy metals affect the cellular DNA and nuclear proteins leading to alteration of cell cycle, carcinogenesis or apoptosis. Increased permissible level of AS in groundwater was found in more than 30 countries. Arsenic affected countries include Argentina, USA, China, Chile, Mexico, Hungary, Vietnam. According to current data AS affects more than nineteen states of India. More than 200 million people worldwide use higher recommended limit of AS contaminated drinking ground water. Ground water is major source, which is used in various purposes like domestic, industrial and agricultural purposes.
Affected districts of WB are North 24-Parganas, South 24-Parganas, Nadia, Hooghly, Malda and Murshidabad where AS concentrations were found to be more than 50μg/l. Globally around 26 million people are potentially at risk for exposed to AS contaminated ground water (>50μg/l).  

Sources and Distribution of Arsenic

In soil occurrence of arsenic at an average concentration of 2-5mg/kg. Volcanic activity is the most important natural sources of AS, which can release huge amounts of AS into the atmosphere. Other sources of AS include the erosion of the rock or soil, forest fires and the other anthropogenic sources. Anthropogenic sources aggravate and accelerate the release of naturally occurring AS.

More than 320-mineral species containing AS are found in the nature. In nature, the ores are the most abundant source of AS. The most important ores containing AS are niceolite, realgar, orpiment, lobaltile, arsenopyrite, and tennanates. Arsenopyrite (FeAsS) is the most common mineral contains AS. After weathering of AS mineral, the AS ions adsorbs onto the Fe (III), and Mn (IV) oxide-hydroxide phases. The AS bearing minerals constitute the source of the AS in natural water.

Arsenic trioxide is the by-product from dust and residues produced during gold and copper smelting operations. Anthropogenic industrial sources contribute to the release of arsenic directly into the environment.

Forms of Arsenic

Out of three allotropic forms, most stable form is silver-gray brittle crystalline solid. The metallic AS is brittle, odourless and tasteless, tarnishes rapidly in air and when heated it rapidly oxidized to form arsenic-trioxide. Non-metallic form is less reactive and dissolves when heated with acids and alkalis. Normally AS is found in four valence states −3, 0, +3, and +5. AS is a naturally occurring metalloid, (i.e., metalloid is a substance that is not a metal but shares many qualities with metals) component of the earth’s crust. Naturally occurring AS react with oxygen or other molecules present in the air, water, or soil to form various reactive compounds.

Arsenic occurs in two forms, inorganic and organic forms. Inorganic forms are most pentavalent state than the organic form. Inorganic AS is prevalent in two forms such as trivalent or the AS\textsuperscript{III} (arsenic tri- oxide, arsenic-trichloride and arsenites) and pentavalent or AS\textsuperscript{V} (Arsenic-pentoxide). The AS\textsuperscript{III} occur in the nature at low levels mostly combined with oxygen, chlorine, and sulphur is called inorganic AS compounds. In the soil it is present in sulphide form and arsenate minerals. It also found in the copper and lead ore deposits, in water, and in industry it is found as gas, which is very much toxic when inhaled. Inorganic forms are much more poisonous to most animals, plants, and humans than the organic AS and disturb the cellular metabolic function.

Combination of the element AS with organic compounds is often known as arsenical organic compounds. Organic compounds of AS and trimethyl arsionium salts are marine in origin. Most often organic AS has commercial application. It is used in making glass (H\textsubscript{3}AsO\textsubscript{4}), insecticides [(NaCH\textsubscript{3}HAsO\textsubscript{3})\textsubscript{3}, (Na\textsubscript{2}CH\textsubscript{3}AsO\textsubscript{3})\textsubscript{3}], weed killers and other compounds. Organic AS is not poisonous for humans, but it may be poisonous when it consumed at high concentrations. During the 18\textsuperscript{th} to 20\textsuperscript{th} centuries, many AS compounds were in use as medicines and green pigment. During World War I, many organic forms were developed and few forms like arsenobetaine or arseneochlorine are found in seafood.

| Organization/ Region | Maximum permissible value of AS (µg/L) | Effective year |
|----------------------|----------------------------------------|----------------|
| WHO                  | 50                                     | 1981           |
| WHO                  | 10                                     | 1993           |
| US EPA               | 50                                     | 1942           |
Toxicokinetics and Metabolism
Permissible Limit of Arsenic Consumption
WHO recommended permissible value for total AS concentration is 0.01 mg/L\(^9\) and for USEPA is 0.05 mg/L. The permissible limit of AS in India and Bangladesh is at 0.05 mg/L based on an earlier report of WHO\(^{20-22}\) are presented in Table-1.

Exposure, Absorption and Metabolism of Arsenic
About 97% exposure to AS occurs through our oral intake of contaminated ground water and food. Absorption of ingested and inhaled AS occurs mostly in the GI tract (45-75)%, lungs and skin. In the GI tract, small intestine is the major site for absorption of AS.

Absorbed AS binds with haemoglobin (Hb) of red blood cells (RBC), after binding with Hb, it is transported to most of the tissues, especially in the liver, kidney, lungs, testis, and skin where it is methylated.\(^{23}\) Compounds of AS can crosses the blood-brain and the placental barrier. Mainly accumulation of AS occur in the keratin and sulfhydryl groups rich tissues. Accumulation of inorganic AS compounds takes place in the epididymis, thyroid gland and lenses of the eyes.

The AS is eliminated mainly through urine as mixture of inorganic, mono-methylated, and di-methylated form. Lesser amounts of elimination of AS occurs via skin, hair, nails, breast milk.

Presence of intestinal bacteria and pH can influence the amount of absorbed AS which undergoes hepatic biomethylation (Fig.1). Metabolism plays an important role for AS toxicity. AS metabolised by reduction and methylation reactions, catalyzed by glutathione-S-transferase \(\omega-1\) (GSTO1) and arsenite methyl-transferase (As3MT). In this methylation process, it is enzymatically converted to methylated arsenicals, which is the end product of the AS metabolism and the biomarker of the chronic AS exposure.\(^{24}\) MMA and DMA are happened before it is expelled through the urine. Variation in AS toxicity depends on its oxidative or reductive state. The monomethyl arsanic acid (MMA\(^V\)) and dimethyl arsenic acid (DMA\(^V\)) are eliminated through urine but MMA\(^{III}\) remains inside the cell as an intermediate product. MMA\(^{III}\) is highly toxic form of AS compared to the others.\(^{26}\)

**Table 1:**

| Country              | Permissible Limit | Year  |
|----------------------|-------------------|-------|
| US EPA               | 10                | 2006  |
| India                | 50                | 1950  |
| India                | 10                | 2012  |
| Bangladesh           | 50                | 1950  |
| Australia            | 7                 | 1996  |
| Canada               | 10                | 2006  |
| Mexico               | 50                | 1994  |
| German Drinking Water Ordinance | 10 | 1996 |
| UK                   | 50                | 1981  |

Fig. 1: Mechanism of AS metabolism showing arsenate reduction to arsenite and methylation. (GSH, glutathione; GST, glutathione S-transferase; SAHC, S-adenosylhomocysteine; SAM, S-adenosylmethionine). (Adapted from Klaassen (2008)).
Arsenic Toxicity
Toxicity of AS on human health mainly depend on its valency, state of oxidation (either as arsenite or arsenate), rate of absorption, frequency and route of intake, exposure time and bio availability. AS\textsuperscript{III}, MMA\textsuperscript{V}, or DMA\textsuperscript{V} are higher toxic than AS\textsuperscript{V}, MMA\textsuperscript{V}, or DMA\textsuperscript{V}. Sodium arsenite (LD50, is 15-44 mg/kg) is about 4-5 times more toxic than Sodium arsenate (LD50 is 112-175 mg/kg). LD50 value of pentavalent organic arsenicals is MMA (960 mg/kg), DMA (650 mg/kg) and 40-100 times less toxic than arsenite.\textsuperscript{77-80} The toxic mechanisms of AS is much complex.\textsuperscript{29-31} Toxicity is affected by its solubility, oxidation state, as well as other internal and external factors. The molecular toxic capacity of AS is usually coupled with its bio transformation mechanisms (Fig. 2). The formation of methylated products of arsenite AS\textsuperscript{III} causes increased genotoxicity and production of reactive oxygen and/or nitrogen species.\textsuperscript{32-35}

Fig. 2: Schematic representation of mechanisms of AS induced genotoxicity. (Adopted from Minatel, B.C. & Sage, A.P. Environment International, 2018, 112, 183-197.) [S-Adenosyl methionine (SAM); S-Adenosyl Homocysteine (SAHC).

Fig. 3: Transmission of AS among plants, animals and humans.
Biological Effects Of Arsenic On Plants And Human

Arsenic is widely present in the soil, groundwater and plants. Biological effects of AS on living organisms occur through bioaccumulation and biomagnifications (Fig.3).

Effects of Arsenic on Plants

AS is not an essential element for plant growth but it can accumulate in plants to toxic levels. Normally, AS uptake by plant depends on the total concentration and form of AS in the soil. In general, plants take up the AS^+ through the roots via phosphate (Pi) transporters. Inside the plant tissue, it produces oxidative stress by generation of reactive oxygen species (ROS) like superoxide radical (O_2^-), hydroxyl radical (OH), and hydrogen peroxide (H_2O_2). ROS is dangerous for cellular metabolism and leads to the irreparable damage to DNA, proteins and lipids and leads to change in morphological, physiological, biochemical, molecular and cellular functions (Table 2).

Table 2: The effects of AS toxicity on plants

| Effect of Arsenic on plants |
|-----------------------------|
| **ROOT**                     |
| Morphology of plant |
| • Structural changes in the root cells. |
| **STEM**                     |
| Growth and development |
| • Reduced the size of main root extension and proliferation. |
| Functional development |
| • Altered expression of transporter genes. |
| **LEAVES**                    |
| • Decreased cross sectional area available for water transport. |
| • Shortens the size of vessels and trachieds. |
| • Reduced leaves number. |
| • Chlorotic appearance of the leaf. |
| • Reduced stomatal conductance. |
| • Leaf senescence. |
| • Leaf necrosis and defoliation. |
| • Chloroplast membrane disintegration |
| • Rate of Photosynthesis decreases. |
| • Disturbances in the rate of transpiration. |

Effects of Arsenic on Human Health

Arsenic toxicity depends on the amount and form of AS intake. Inorganic AS is highly toxic carcinogen, and is the most significant contaminant in drinking-water globally. The AS can cause various adverse impact on different organ systems of the body. Such organ systems are integumentary, cardiovascular, respiratory, gastrointestinal, endocrine, reproductive, neurological, developmental abnormalities and cancerous. Depending on the level of exposure, its toxic effects may be acute or chronic. Acute AS toxicity occurs when a single large dose of AS cause severe symptoms. Initial symptoms of acute AS poisoning are muscular pain and weakness following severe nausea, vomiting, abdominal pain, diarrhoea, cyanosis, cardiac arrhythmia, confusion and hallucinations. Other acute poising include bone marrow depression leading to anaemia and leucopenia, cold clammy skin, renal failure, encephalopathy and peripheral neuropathy like impaired sensation, movement of gland or organ function are also reported.

Inhalation of AS gas leads to acute problems like cough, bronchitis, shortness of breath. AS ingestion for a prolonged period leads to an accumulation of AS in the body causing chronic AS toxicity with various clinical manifestations collectively called arsenicosis. Arsenicosis leads to keratosis, pigmentation (hyperpigmentation / hypopigmentation) of feet,
hands, fingers. Chronic AS toxicity results in multiorgan system disease and the most serious consequences being the malignancy. AS increase the incidence of carcinogenicity in organs like skin, lung, kidney, urinary bladder, prostate, and liver. Various organ systems of the body are affected by chronic arsenic exposure with inorganic AS. This article mainly focuses to explain the effect of arsenic on human health on two headings- cancerous and non-cancerous effects.

**Cancer Effects**
Carcinogenic property of AS compounds was first identified more than a century ago. Since 1980, AS was listed as a human carcinogen. AS is a unique carcinogen for which the carcinogenic risk arises from both the ingestion and inhalation. People exposed to AS contaminated drinking water for more than 40-years develops urinary tract cancer more often than people with less than 40-years of exposure. There is a large gap between the exposures of AS on clinical manifestation of cancer. This gap period is called the latent phase. Ingestion of iAS causes lung cancer, and long term ingestion of iAS is linked risk of urinary bladder cancer, skin cancer and also GI tract, kidney and prostate

| Target organ | Source | Result | Population location | Reference Number |
|--------------|--------|--------|---------------------|------------------|
| Skin Cancer  | Well water | Increased mortality | Taiwan | 66 |
| Drinking water | Increased mortality | South-West Taiwan | 67 |
| Drinking water | Increased mortality | Taiwan | 68 |
| Drinking water | Increased mortality | Mexico | 69 |
| Drinking water | Increased mortality | Chile | 70 |
| Drinking water | Increased mortality | USA | 71 |
| Drinking water | Increased mortality | USA | 72 |
| Drinking water | Increased mortality | USA | 73 |
| Drinking water | Increased mortality | China | 74 |
| Lung Cancer   | AS exposed area | Increased mortality | South-West Taiwan | 77 |
| Drinking water | Increased mortality | Taiwan | 78 |
| Drinking water | Increased mortality | Northern Chile | 61 |
| Drinking water | Increased mortality | Chile | 70 |
| Drinking water | Increased mortality | U.S.A | 79 |
| Local water/soil | Increased incidence | Victoria, Australia | 80 |
| Liver cancer  | Drinking water | Increased mortality | South-West Taiwan | 67 |
| Drinking water | Increased mortality | South-West Taiwan | 87 |
| Drinking water | Increased mortality | South-West Taiwan | 85 |
| AS contaminated region | Increased mortality | Northern Chile | 88 |
| Drinking water | Increased mortality | Chile | 16 |
| Local water/soil | Increased incidence | Victoria, Australia | 80 |
| Drinking water | Increased mortality | West Bengal, India | 89 |
| Bladder cancer | Drinking water | Increased mortality | South-West Taiwan | 67 |
| Drinking water | Increased mortality | South-West Taiwan | 87 |
| Drinking water | Increased mortality | Taiwan | 92 |
| AS exposed area | Increased Mortality | South-West Taiwan | 77 |
| AS contaminated region | Increased mortality | Northern Chile | 88 |
| Local water/soil | Increased incidence | Victoria, Australia | 80 |
| Drinking water | Increased mortality | USA | 71 |
Skin Cancer
There is a positive link between AS exposure and skin cancer like Bowen’s disease, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Arsenite has an important role on UV-induced skin cancer. Skin cancer probably occurs through the effect on DNA repair and DNA methylation. The AS interacts with Fas/Fas ligand pathway (also known as Apo1 or CD95), results alterations in the transcription factor NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cell) and AP-1 (Activator protein 1) activity. These transcription factors produce various inflammatory cytokines. NFAT (Nuclear factor of activated T-cells) transcription factor is linked with cancer. Epidemiological evidence suggest that the association between AS and cancers of skin and internal organs (Table 3).

Lung Cancer
Lung cancer is one of the serious forms of cancer associated with AS ingestion. Patients who were previously suffering from either hyper pigmentation or hyperkeratosis or Bowen’s disease are found to be more prone to have lung cancer. Lung cancer is also associated with occupational exposure to AS via inhalation, very little research data is available showing the association between ingested Arsenic and lung cancer. Lung adenocarcinoma is the most common and also AS-induced lung tumors are observed (Table 3).

Liver Cancer
Liver is one of the important internal organs affected by chronic exposure to arsenic. Direct association between AS exposure and human liver cancers was established. Epidemiological studies reveal that chronic AS exposure causes liver diseases including hepatomegaly, hepatportal sclerosis, liver fibrosis and cirrhosis of liver, and liver cancer. Liver is the target organ for AS-induced carcinogenesis and develops hepatocellular carcinoma (HCC). Chronic exposure to AS is also linked with an increased prevalence of liver hepatitis/cirrhosis. The potential mechanism of AS induced carcinogenesis is oxidative DNA damage, acquired tolerance to apoptosis and enhanced cell proliferation, altered DNA methylation and genomic instability.

Bladder Cancer
Chronic intake of high levels of inorganic AS shows the strong associations and dose-response relationships between bladder cancer and urothelial carcinoma of the bladder (UCB). Chronic AS exposure leads to the expression of inflammatory enzyme cyclooxygenase-2 (COX2) and the COX2-derived prostaglandin E2 (PGE2). COX2 and PGE2 pathway causes the multistep development of cancer. Majority of UCB occurs due to expression of COX2.

Prostate Cancer
Little research study shows the strong linked between ground water arsenic toxicity and prostate cancer. In vitro study shows that AS can also causes prostate cancer cell progression. It also proved that there is a positive relation in dose-response relationships between arsenic level and age-adjusted prostate cancer mortality.

Non-Cancer Effects
Effect on Skin
Chronic AS poisoning cause damages to many organ systems of the body. Symptoms of AS toxicity are first manifested in the skin. The first observed effects of chronic AS exposures were non-malignant skin manifestations, which include hyperpigmentation, palmar and solar keratosis. Skin lesions are found to be the most common features of chronic AS exposure. Lesions of skin occur usually years after exposure. The first visible symptoms caused by prolonged ingestion of AS in drinking water is black brown skin pigmentation, called melanosis. If this exposure continues for longer duration, then fine freckles of spotted pigmented changes are also observed, which is known as ‘rain-drop’ pigmentation.
**Effect on Cardiovascular System**

Chronic AS exposure has been linked to cardiovascular disease (CVD), including coronary heart disease (CHD), stroke, peripheral vascular disease (PVD), hypertension, atherosclerosis, ischemic heart disease, vascular disease mortality. Chronic AS poisoning leads to inactivation of endothelial nitric oxide synthase and resulting reduction in generation and bioavailability of NO (Nitric oxide). Increased activity of vascular NOX (NADPH-oxidases) enzymes play a key role in pathogenic redox signalling in vascular disease and hypertension. Arsenite stimulates NADPH oxidase to increase the generation of ROS (Reactive oxygen species). ROS production is the initial step in AS induced endothelial cell proliferation and apoptosis. These two mechanisms proposed for AS-related atherosclerosis.

**Effect on Respiratory System**

Exposure of AS occurs through inhalation has significantly associated with the progression of non-malignant respiratory lung disorders. As a result there are occurrence of chronic bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD), and respiratory disease mortality. AS result the strength of the respiratory muscles decreases, vital capacity, total lung volume capacity also gets decreases. It is observed that those patients with the characteristic skin lesions of chronic AS toxicity have more susceptible for respiratory diseases.

**Effect on Gastrointestinal System**

Due to acute AS poisoning gastrointestinal symptoms are more common. The important clinical features of the acute AS poisoning are burning lips, painful swallowing, thirst, nausea, vomiting, and others abdominal colic diarrhoea. Inorganic AS is ingested into the body by different routes and is metabolized by the liver. In liver, methylation takes place and produces dimethyl-arsenic glutathione, which is stored in the gall bladder and ejected in bile.

**Effect on Excretory System**

The kidneys are the main organ involved in the excretion of AS and its metabolites. The common affected sites are capillaries, tubules and glomeruli. Epidemiologic studies suggest that high AS exposure can be associated with chronic kidney disease (CKD). CKD is associated with reduced GFR (Glomerular Filtration Rate) and increased urinary albumin excretion.

**Effect on Reproductive System**

Globally, AS is recognized as a reproductive toxicant in humans. In males, exposure to AS cause reproductive organ dysfunctions likes reduction in weight of primary and accessory sex organs. AS causes change in plasma concentrations of LH (Leutinizing Hormone) and FSH (Follicular Stimulating Hormone) by inhibiting hypothalmo-pituitary gonadal axis. Reduced plasma LH impairs Leydig cell functions and consequently reduction in testosterone production.

AS toxicity involves with female reproductive system functions and jeopardize it in diverse ways. It causes a serious toxic effect on the primary sex organ of female (ovary). It is associated with suppression of ovarian steroidogenesis, and degenerates ovarian follicular and uterine cells. Sum of all these effects lead to abnormal reproductive functions and pregnancy outcome of a woman.

**Effect on Nervous System**

The AS can alter the integration and co-ordination functions of the brain. The neurotoxic effects of AS appear to be most severe in the developing brain, as AS can cause cellular changes in the brain. Many research studies have been reported that AS exposure can cause impaired functions of neural pathways and causes polyneuropathy, EEG (Electroencephalogram) abnormalities and in extreme cases hallucinations, disorientation and agitation. Cognitive functions disturbances associated with decreased intelligence, verbal coefficients, impairments in learning and memory, changes in behaviour, and confusion.

**Haematological Effect**

Acute and chronic AS exposure may cause change in blood compositions. The reduced RBC count may be due to inhibition of erythropoietin production or by the depression of bone marrow. AS exposure causes the depression of the bone marrow, results decreased RBC and WBC production. AS toxicity may causes changes in the morphological structure of RBC. AS induced changes occur in the RBC membrane integrity and deformability, which contribute to micro vascular occlusion and related peripheral vascular effects.
Immunological Effect
Chronic exposure to AS potentially impair vital immunological functions. Reduced immunological functions lead to increased risk of infections and inflammatory-like diseases. The AS may affect lymphocyte, monocyte and macrophage activity resulting in immune-suppression. Prenatal AS exposure has been associated with reduced thymic index leads to reduced cell-mediated immune function. This indicates that during childhood AS exposure causes arsenic-induced developmental immunotoxicity. Chronic high concentration of AS exposure has been associated with reduced Th1/Th2 secretion of interleukin-2 (IL-2). Both T lymphocytes and macrophages are involved in the initiation of humoral immune response. The AS suppresses T-cell dependent antibody responses. The AS exposure can impair on antibody production and trans-placental IgG transport to neonates.

Arsenic and Diabetes
Chronic high concentration AS exposure has role on the development of diabetes mellitus (DM). Epidemiological study and experimental evidences support the role of iAS in the development of diabetes. The possible mechanisms for the development of DM may be due to iAS interference with insulin-stimulated signal transduction pathway or during acute poisoning, arsenite inhibits pyruvate and α-ketoglutarate dehydrogenases enzymes which are essential for gluconeogenesis and glycolysis. By other mechanism AS could also influence the development of type-2-DM by oxidative stress, inflammation and nonspecific mechanisms.

Conclusion
AS and its compounds are known potent poisons causing widespread environmental contamination. From the above discussion and other research studies, we can conclude that AS is a potent carcinogen. The chronic high concentration AS exposure causes cancer of the skin, lung, liver, kidney, bladder, and prostate gland. Depending upon acute or chronic exposure AS toxicity varies. It increases in premature delivery and decreased birth weights of infants. The possibility of an association between chronic AS exposure and diabetes has implications for research and public health. The experimental and epidemiologic evidence suggest that AS has various toxic effects on different organ systems on human health.

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