Geological Sources of Arsenic and Cancer Risk Associated with The Metalloid- An Overview

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Abstract
Arsenic, a widely prevalent metalloid in the environment, poses significant health risks due to chronic exposure through contaminated water, food, and various human activities. This comprehensive overview highlights the prevalence of arsenic poisoning, particularly in regions like India and Bangladesh, stemming from arsenic-contaminated drinking water. The toxicological impact of chronic arsenic exposure on human health is multifaceted, leading to dermatological, neurological, and organ-related complications. Notably, arsenic exposure has been linked to the development of malignancies such as lung, bladder, liver, kidney, gastrointestinal, and brain cancers. Mechanisms of arsenic-induced carcinogenesis, DNA damage, and associated health conditions are elucidated. Understanding the sources, prevalence, and health impacts of arsenic contamination is crucial for implementing effective mitigation strategies.

Keywords: Arsenic poisoning, Chronic exposure, Carcinogenesis mechanisms

1. Introduction
Arsenic (As), recognized as a metalloid with an atomic number of 33 and a relative atomic mass of 74.92, is widely prevalent in the environment (Fig 1). It is found in both natural and human-made sources, abundant on the Earth's surface, and present in small amounts in water, soil, air, and rock. The main inorganic forms of arsenic include trivalent meta-arsenite (As³⁺) and pentavalent arsenate (As⁵⁺). Trivalent arsenicals are particularly potent due to their interaction with sulfur in proteins. Human exposure to both trivalent and pentavalent forms of arsenic occur chronically through inhalation, ingestion of contaminated food, and the consumption of water containing arsenic [1]. The primary source of arsenic poisoning is the consumption of arsenic-contaminated groundwater, especially prevalent in areas like India, Bangladesh, China, and certain Central and South American countries. Regardless of its specific form, absorbed arsenic is distributed extensively throughout the entire body [2].

Arsenic poisoning is a prevalent issue in numerous locations in India and Bangladesh, primarily stemming from the consumption of arsenic-contaminated drinking water. This contamination has been linked to the occurrence of dermatological and neurological lesions observed in West Bengal and neighboring areas of Bangladesh. In Bangladesh, fifty districts, and in West Bengal, nine districts, exceed the World Health Organization's maximum permissible limit of 50µg/L for arsenic levels in groundwater. The estimated arsenic level surpasses 50 µg/L in approximately 2000 villages across 50 affected districts in Bangladesh and 2600 villages in 9 affected districts in West Bengal. Scientists have analyzed 34,000 and 101,934 hand tube-well water samples from Bangladesh and West Bengal, respectively, using the Hydride Generation Atomic Absorption Spectrophotometer. Results showed that 56% and 52% of samples from Bangladesh and West Bengal contained arsenic levels above 10 µg/L, while 37% and 25% exceeded the limit of 50 µg/L. In a preliminary study, clinical examinations were conducted on 18,000 individuals in Bangladesh and 86,000 in West Bengal residing in arsenic-affected districts, revealing that 3,695 in Bangladesh and 8,500 in West Bengal displayed arsenical dermatological features. Symptoms of chronic arsenic toxicity typically developed after 6 months to 2 years of exposure [3].
Chronic arsenicosis resulting from drinking arsenic-contaminated water is complex and depends on various factors. The major determinants for arsenic toxicity include oxidation state, charge at physiological pH, biomethylation extent, electrostatic interactions with macromolecules or enzymes, and several pharmacokinetic factors such as absorption, distribution, metabolism, protein binding, and excretion. Previous reports indicate that chronic arsenic exposure can induce various toxicities, leading to severe organ dysfunctions. Arsenic and its methylated metabolites can cross the placenta, causing long-term organ toxicities that result in impaired fetal growth, fetal loss, or post-birth infant mortality. Early-life exposure also leads to serious effects such as malignancies and syndromes [4].

Exposure to arsenic has been linked to the development of various malignancies and solid tumors, such as lung and bladder cancers. The process of arsenic-associated carcinogenesis appears to depend on factors such as exposure levels, genetic predisposition, and geographical location. Additionally, chronic conditions like hypertension, cardiovascular disease, and diabetes have been observed in association with arsenic exposure. Furthermore, chronic exposure to arsenic has been reported to result in long-term memory loss and alterations in hormonal regulation [5].

**Arsenic and arsenic-containing compounds**

Examining arsenic compounds from a biological and toxicological perspective reveals three main groups: inorganic arsenic compounds, organic arsenic compounds, and arsine gas. Arsenite dominates under reducing conditions, while arsenate is the stable form in oxygenated environments. Arsenic is present in over 200 mineral species, with 60% comprising arsenate and 20% sulfide and sulfosalts, and the remaining 20% consisting of arsenides, arsenites, oxides, and elemental arsenic. Commonly associated with various mineral deposits, especially those with sulfide mineralization, arsenic exhibits diverse forms.

The most prevalent trivalent inorganic arsenic compounds include arsenic trioxide, sodium arsenite, and sodium trichlorite. Conversely, the most common pentavalent inorganic arsenic compounds encompass arsenic pentoxide, arsenic acid, and various arsenates (such as sodium arsenate, lead arsenate, and calcium arsenate). Among the frequently encountered organic compounds are arsenic acid, methylarsonic acid, dimethylarsinic (cacodylic acid), and arsenobetaine. Arsenic species display varying levels of toxicity and exhibit distinct biochemical and environmental behaviors. Arsenate [As(V)] is the prevailing environmental form of inorganic arsenic, while arsenite [As(III)] is recognized as more toxic. Upon heating in air, arsenic oxidizes to arsenic trioxide (As$_2$O$_3$), emitting fumes with a garlic-like odor. As$_2$O$_3$ is also a by-product in the metal smelting process. Elemental arsenic remains insoluble in water, and the solubility of arsenic salts fluctuates based on pH and the ionic environment [6].

Human activities, including mining, industrial smelting of metals, coal-based power generation, and the use of arsenic-containing pesticides and herbicides, contribute to environmental contamination by arsenic. Exposure to arsenic can result from various sources such as the ingestion of contaminated food, consumption of arsenic-contaminated water, use of medications, inhalation of dust particles or aerosols, and direct skin contact. To prevent exposure and mitigate the harmful effects of arsenic, it is crucial to comprehend the sources and levels of arsenic contamination.

**Drinking Water Contamination**

The primary source of human exposure to arsenic compounds is water. Arsenic-bearing minerals contaminate underground water and aquifers during oxidation processes, releasing arsenic into water bodies. The confluence of the Ganges and Brahmaputra rivers exhibits seasonal variations in dissolved arsenic concentrations, with the highest levels observed during the monsoon season. Arsenic is present in suspended particulate matter resulting from flooding and runoff from agricultural lands irrigated with arsenic-rich groundwaters. Another source of arsenic contamination in groundwater is the reduction of Fe/As oxyhydroxides.

Bangladesh and West Bengal are among the most severely affected regions globally, with arsenic concentrations in groundwater reaching up to 3200 μg/L in certain areas. The prevalent species found in water are inorganic forms, existing in stable trivalent and pentavalent forms. The trivalent form is predominant in groundwater, while the pentavalent species are more prevalent in surface water [7, 8].

**Arsenic exposure**

**Arsenic contaminated food**

Food is also source of Arsenic exposure, specifically infants in early stages. Studies carried in different countries to assess the total dietary arsenic have shown that in areas where there is no endemic arsenic
contamination, intakes between 8 and 345 μg/day are observed. Fish food or sea food constitute the group of major contributors to arsenic intake. In these foods Arsenic exposure through food, particularly in infants, is a notable concern, even in areas without endemic contamination. Studies conducted worldwide reveal total dietary arsenic intakes ranging from 8 to 345 μg/day. Seafood, notably fish, emerges as a significant contributor, with arsenic concentrations often surpassing 1 mg/g and occasionally exceeding 10 mg/g. Various arsenic compounds, such as arsenobetaine, DMA, MMA, TMAO, AC, TMA,

Fig 2. dissolved arsenic concentrations and particulate As concentrations at the Ganges–Brahmaputra confluence [9].

and arsinosugars, have been identified in these foods. The typical concentration of inorganic arsenic is 0.1 mg/g. Crustaceans and bivalves show arsenic concentrations from 0.001 to 4.5 mg/kg, while edible algae can accumulate up to 141 mg/kg. In terrestrial animal foods, AsIII and AsV contents are reported to be below 0.05 mg/g. Arsenic content in rice products varies from 0.02 to 0.56 mg/kg, with certain rice samples reaching up to 1.8 mg/kg. MMA levels can reach 0.015 mg/kg, and DMA levels range from 0.486 to 0.539 mg/kg [10].

Soil Contamination

The primary origin of arsenic in soil stems from the inherent composition of the parent soil. Several factors, including the geological makeup of parent rock materials, volcanic activity, historical weathering processes, biological interactions, sorption, transportation mechanisms, and precipitation, collectively shape the characteristics of arsenic in soil. The natural arsenic content in soils exhibits considerable variability, ranging from 0.01 to over 600 mg/kg. Within the soil environment, arsenic undergoes various biotransformation processes, including the biosynthesis of organoarsenic compounds, redox conversions between arsenite and arsenate, as well as reduction and methylation reactions. Due to the susceptibility of trivalent arsenicals to oxidation, pentavalent inorganic arsenic forms are more prevalent in soil. It is noteworthy that the absorption of arsenic through the skin is constrained in the presence of arsenic-contaminated soil [11].

Exposure due to medication

With a history spanning over 2400 years, arsenic has been employed in the treatment of various ailments, including toothaches, abscesses, and ulcers. In 1786, Fowler’s solution, a 1% potassium arsenite solution, was formulated and became a therapeutic agent for conditions such as malaria, syphilis, asthma, chorea, eczema, and psoriasis. Notably, it was reported to reduce white blood cell count in leukemia patients and served as a tonic for anemia. Fowler’s solution found use in treating rheumatism, dermatitis herpetiformis, Hodgkin’s disease, pemphigus, and pernicious anemia [12].

In 1910, Paul Ehrlich introduced Salvarsan, an organic arsenical, for treating syphilis and trypanosomiasis. Traditional Chinese medicine continues to utilize arsenic derivatives in the treatment of painful tooth conditions. Despite the organic arsenic compound melarsoprol remaining the drug of choice for treating the protozoan parasite disease trypanosomiasis, the use of arsenic derivatives in medical applications has significantly diminished due to their toxic properties [13].
Occupational Exposure to Arsenic

Arsenic finds application in various sectors, including its use in wood preservatives, herbicides, insecticides, pesticides, fungicides, high-emitting diodes, and even in its elemental form \cite{14,15}. The extent of airborne arsenic inhalation depends on factors such as the compound's characteristics, matrix composition, and particle size distribution. Valuable insights into the toxicity of arsenic have been gained from research on orchard workers who fell ill after exposure to lead arsenate, a pesticide used in apple and cherry orchards \cite{16}. This research sheds light on the health risks associated with arsenic exposure, especially in occupational settings such as agriculture.

Nutritional aspect

The nutritional need for arsenic remains unknown. However, akin to other toxic metals, the metabolism of arsenic is thought to involve the transformation of its most potentially harmful form into a less toxic one. This transformed form may either be accumulated within the cell or excreted from it. Notably, unlike many other toxic metals such as mercury and cadmium, arsenic does not seem to undergo biomagnification through the food chain \cite{7,17}.

Biomethylation

Inorganic compounds containing arsenic are highly reactive and pose potential toxicity to both humans and other animals. The primary mechanism for detoxifying arsenic is believed to involve biomethylation, a process observed in a variety of organisms, including yeast, fungi, algae, plants, and animals \cite{18}. Arsenic, an indispensable component in semiconductors, exposes workers in the manufacturing of arsenic-containing products to potential toxicity through inhalation or dermal contact \cite{14}.

The use of arsenic for tick control in South Africa dates back to 1893, and since then, arsenic, in the form of the sodium salt of arsenous acid, has been employed for various purposes. Additionally, exposure to arsenic occurs through processes like smelting and coal burning, generating stack dust and flue gas that contribute to soil and water contamination.

Inorganic arsenic is methylated to monomethylarsonic acid (MMA) and then to dimethylarsinic acid (DMA) by the methyl donor S-adenosylmethionine (SAM) in higher organisms. Reduction of pentavalent arsenic to trivalent arsenic is an important step in controlling the rate of arsenic metabolism. Reports show that DMA excretion level is high in higher organisms, inorganic arsenic undergoes methylation, first to monomethylarsonic acid (MMA) and then to dimethylarsinic acid (DMA), facilitated by the methyl donor S-adenosylmethionine (SAM). The reduction of pentavalent arsenic to trivalent arsenic plays a crucial role in regulating the rate of arsenic metabolism. Reports indicate that the excretion of DMA becomes prominent after a few days, during which the excretion of the inorganic form significantly increases. This observation suggests the involvement of two consecutive methylating enzyme activities in this methylation process \cite{19}.

Pathophysiology of Arsenic Toxicity

Prolonged exposure to arsenic is associated with a range of cardiac dysfunctions, including atherosclerosis, hypertension, ischemic heart diseases, ventricular arrhythmias, peripheral arterial disease, impaired microcirculation, and coronary heart disease. Arsenic induces cytotoxic effects on cardiomyocytes by generating reactive oxygen species (ROS), comprising superoxides and hydrogen peroxide. These ROS are produced through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the plasma membrane of vascular endothelial cells and vascular smooth muscle cells.

The resulting ROS contribute to the loss of cardiac actin, reduction in size, and damage to the nuclei. This series of events disrupts the vascular extracellular matrix, ultimately leading to apoptosis through mitochondria-dependent caspase-3 signaling \cite{21,22}. Furthermore, the ROS generated by NAD(P)H oxidase, when combined with nitric oxide (NO), form the potent oxidant peroxynitrite, leading to the up-regulation of inflammatory mediators like cyclooxygenase-2. ROS also triggers the expression of genes associated with atherosclerosis, including heme oxygenase-1, monocyte chemo-attractant protein, and interleukin-6. Notably, a striking resemblance exists between arsenic-induced hypertension and atherosclerosis, with a decrease in nitric oxide bioavailability identified as a contributing factor \cite{20}.

Hepatic Toxicity

Liver is the major organ involved in arsenic metabolism and also main target for arsenic to cause toxicity. The highest level of arsenic is accumulated in the liver. Arsenic-induced hepatotoxicity is - 849 -
manifested by increased levels of alanine aminotransferase and aspartate aminotransferase. Arsenite exposure increases ROS production, which consequently enhances the level of lipid peroxidation, other oxidative stress-related biomarkers, and cellular damage in hepatic tissues. Subacute and chronic exposure of arsenic has been reported to increase ROS level, and decrease the GSH/GSSG ratio and antioxidant enzyme activities along with increased lipid peroxidation in hepatic tissues. Chronic exposure also causes increased hepatic collagen accumulation and can be correlated with increased levels of IL-6. Pyruvate dehydrogenase is vulnerable to ROS induced due to arsenic and its inhibition could cause imbalance in carbohydrate metabolism as well as diabetes. 8-OHdG found to be increased in arsenic induced hepatocarcinogenesis which is also marker for DNA damage [24].

Renal Toxicity

Chronic arsenic exposure through drinking water is associated with renal problems. Another primary target organ of arsenic is the kidneys. Arsenite exposure increases ROS production, which inturn increases the level of lipid peroxidation, other oxidative stress-related biomarkers, and cellular damage in renal tissue. Arsenic causes renal failure and renal dysfunction, creatinine levels also found to increase in chronic exposure cases. The mechanisms are not clear yet. Direct involvement of kidney in arsenic excretion, hypotensive shock, hemoglobinuric or myoglobinuric tubular injury suggests the association of these processes with arsenic exposure [25].

Chronic skin manifestations

Chronic skin manifestations include hyperpigmentation with superimposed guttate hypopigmentation described as “raindrops on a dusty road,” punctate hyperkeratoses on the palms and soles, diffuse alopecia, blackfoot vascular occlusive disease, Bowen’s disease, squamous cell carcinoma, and basal cell carcinoma. Blackfoot disease is common arsenic affected areas and typically affects the lower extremities and results in gangrene if left untreated. The latency period for the development of arsenical skin disease ranges from 30 to 50 years. The development of skin cancer in sun-protected areas is especially concerning for the existence of chronic arsenic exposure. These cutaneous manifestations serve as a surrogate marker for associated diseases such as hypertension, ischemic heart disease, atherosclerosis, peripheral vascular disease, diabetes mellitus, peripheral neuropathy. Arsenical keratoses are precancerous lesions that begin as yellow pinpoint hyperkeratotic papules ranging in size from 0 to 2 mm, commonly seen on pressure points of the palms and soles such as the lateral borders of the hands. These lesions are commonly reported in patients with chronic medicinal exposure rather than that from the workplace [26].

Squamous cell carcinoma induced by arsenic exposure tends to display a higher level of aggressiveness compared to its counterpart caused by chronic exposure to ultraviolet (UV) radiation. Studies have revealed that approximately 33% of untreated arsenical squamous cell carcinoma cases exhibit metastatic behavior. Arsenical keratoses, which are potential precursors to squamous cell carcinoma, often manifest with symptoms such as pain, bleeding, fissuring, and eventual ulceration. The risk factors associated with the progression of these keratoses to squamous cell carcinoma include early-life exposure to arsenic, the presence of multiple lesions, and the involvement of acral sites. These findings underscore the importance of recognizing and addressing the specific risks associated with arsenic-induced squamous cell carcinoma.

Respiratory Disease

In a study conducted in Kolkata, West Bengal, involving 156 cases of chronic arsenic toxicity associated with arsenical skin lesions resulting from the consumption of arsenic-contaminated groundwater, symptoms of lung disease were documented. Among the cases, 89 individuals reported experiencing chronic cough, both with and without expectoration, while 45 cases exhibited chest signs indicative of lung disease. Further investigation through lung function tests conducted on 17 patients revealed that nine of them displayed features consistent with restrictive lung disease, and seven cases exhibited a combination of obstructive and restrictive lung disease [27]. These findings underscore the association between chronic arsenic exposure and respiratory symptoms, emphasizing the importance of addressing the impact of arsenic contamination on lung health in affected populations.

Arsenic and Bladder Disease

studies on populations with high arsenic exposure in locations like Taiwan, Argentina, Japan, and Chile suggest an increased likelihood of urinary tract cancer. The evidence strongly supports a connection between arsenic exposure in drinking water, especially at concentrations surpassing 300–500 μg/L, and an elevated risk of bladder cancer. However, the association with arsenic levels below 200 μg/L, except for smokers, remains a point of contention.
While the exact mechanisms through which arsenic contributes to bladder cancer are not fully elucidated, proposed pathways involve interactions with thiol groups. Furthermore, there are documented instances of heightened levels of reactive oxygen species (ROS), oxidative DNA damage, apoptosis, increased cell proliferation, altered DNA methylation, and genomic instability associated with arsenic exposure and bladder cancer in some cases [28]. These findings emphasize the intricate relationship between arsenic exposure and molecular processes that may contribute to the development of bladder cancer, highlighting the necessity for continued research in this field.

**Hematological Effects**

Chronic arsenic poisoning induces haematological abnormalities. A characteristic pattern of anemia, leukopenia, and thrombocytopenia was found in 55 individuals exposed to arsenic in drinking water in Niigata Prefecture in Japan for approximately 5 years, half of the subjects having arsenical skin lesions. Hemoglobin (Hb) is one of the main constituents of red blood cells and its interaction with arsenic is well studied. Thiols groups in Hb reacts with arsenic reducing its binding affinity to oxygen. Reports also suggests that Hb has a higher binding affinity to arsenic compared to oxygen. It is also suggested that inhibition of ALAD ALAD (δ-aminolevulinic acid dehydratase) results in an accumulation of ALA, which may play a role in arsenic-mediated ROS generation in blood. Arsenic exposure influences GSH levels in blood [29].

**Oxidative Stress**

An imbalance between the production of cellular oxidant species and the capability of the cells to produce antioxidants results in oxidative stress. Oxidative stress creation is one of the carcinogenesis processes and arsenic is proposed to induce skin carcinogenesis by induction of oxidative stress/reactive oxygen species (ROS). Arsenic induces morphologic alterations in mitochondrial integrity, which leads to inactivation of mitochondrial enzymes and loss of mitochondrial membrane potential. Arsenic may serve also as a bypass for electrons from the respiratory chain that facilitate the formation of superoxide anion radicals and generation of ROS (H$_2$O$_2$, O$_2$, ROO, OH, and NO) as well as a reduction in activity of an important cellular antioxidant, glutathione (γ-glutamylcysteinylglycine, GSH). Arsenite reduces oxygen directly to H$_2$O$_2$ and/or formation of arsenic peroxy radicals, which are mediators of DNA damage, mitosis disrupters, and apoptosis promoters. The indicators of arsenic-induced oxidative stress include high levels of 8-hydroxydeoxyguanosine, lipid peroxides, glutathione, heme oxygenase-1, and peroxiredoxin 1. In this regard, mitochondria-mediated production of hydroxyl and hydrogen peroxide plays a key role in the reduction of intracellular thiols, particularly glutathione [30].

Chronic arsenic exposure also depletes stores of the antioxidant nitric oxide (NO) through its reaction with the superoxide anion and as a consequence of NO synthase (NOS) uncoupling. Arsenic has been found to uncouple the NOS enzyme by reducing levels of its cofactor, tetrahydrobiopterin. Unchanged concentrations of L-arginine in the setting of decreased tetrahydrobiopterin shift NO synthase production from NO to superoxide instead [31].

**Arsenicalosis and Cancer**

The evidence of carcinogenicity in humans from exposure to arsenic is based on epidemiological studies of cancer in relation to arsenic in drinking water.

**Skin Cancer**

Skin cancer is a commonly observed malignancy related to drinking of arsenic-contaminated water. Skin cancer due to chronic arsenic exposure occurs as Bowen’s disease (intraepithelial carcinoma, or carcinoma in situ), basal cell carcinoma, and squamous cell carcinoma. Skin cancer might arise in the hyperkeratotic areas or might appear on non-keratotic areas of the trunk, extremities, or hand [6, 18]. Features of Bowen’s disease have been described earlier. Arsenic-related basal cell carcinoma appears to be deep ulcerative or superficial type as those of ordinary type of basal cell carcinoma. Histologically, the cells have scanty and ill-defined cytoplasm. Nuclear atypy and giant cells are not ordinarily found. The size and gross appearance of epidermoid carcinoma varied greatly, some forming fungating masses measuring up to 5 by 5 cm and some causing large crater-like ulcers with elevated margins measuring up to 6 cm in diameter [26].

**Urinary Bladder Cancer**

The working group of the IARC evaluated ecological studies in Taiwan, Chile, Argentina, and Australia, cohort studies from Taiwan, Japan, and the USA, and case–control studies in Taiwan, the USA, and Finland and found evidence of increased risk for urinary bladder cancer associated with arsenic in drinking water. The report of bladder cancer associated with drinking arsenic-contaminated water.
water was published from the province of Cordoba in Argentina where 11% of cancer deaths were caused by this cancer. An ecological mortality study for bladder cancer was conducted in Chile in Region II (arsenic endemic region) and in Region VIII (non-arsenic endemic area) for the period 1950–1992 and the SMR was found to be 10.2 (95% CI: 8.6–12.2). In Taiwan, the evidence of increased occurrence of bladder cancer due to arsenic was supported by case–control and cohort studies within the exposed communities that demonstrated evidence of a dose–response relationship with levels of arsenic in drinking water. There was also evidence of increased risks of bladder cancer from a small cohort study in Japan of persons drinking from wells that had been highly contaminated with arsenic wastes from a factory. The findings of epidemiological studies are consistent with a strong association of arsenicism with bladder cancer [32, 33].

**Lung Cancer**

On the basis of ecological studies using mortality data in Taiwan, Chile, Argentina, and Australia, cohort studies in Taiwan, Japan, and the USA, and case–control studies in Taiwan and Chile, a strong association of lung cancer has been observed in populations with high arsenic exposure. In an ecological study, increased mortality from lung cancer was observed in men and women in 1968–1982 in an area endemic for blackfoot disease in Taiwan. There was an exposure–response relationship between the SMR of lung cancer and the prevalence of blackfoot disease. Elevated SMRs (about three) were observed for lung cancer for both sexes in Region II of Chile using national rate as a standard [34].

**Liver cancer**

Ingestion of arsenic has been linked to hepatocellular carcinoma (HCC), which is another type of malignant transformation of hepatocytes. Malignant transformation of the sinusoidal endothelial cells is referred to as angiosarcoma, and is linked to exposure to inorganic arsenic as well as vinyl chloride, Fowler’s solution, anabolic steroids, and Thorotrast. Chronic arsenic exposure leads to liver injury when the cell’s organelles are damaged. Chronic arsenic exposure has been associated with a variety of hepatic dysfunctions including macrovesicular steatosis, phospholipidosis, cholestatic lesions, steatohepatitis, granulomatous reactions, fibrosis, cirrhosis, vascular lesions, and/or neoplasms, depending on the dose and exposure conditions. Arsenic has been reported to enhance hepatic morphological and biochemical changes in phenobarbital-pretreated rats. Hydrophic degeneration, total loss of glycogen, necrosis in some centrolobular zones, and an increase in lipid vacuoles around the periporal area have been observed. HCC have been observed in different populations exposed to elevated levels of arsenic in drinking water including Japan, Mexico, Chile, Germany, Argentina, Taiwan, China, India, and Bangladesh. It is suggested that arsenic could be interacting with other risk factors, including hepatitis B and C infection, aflatoxin, alcohol abuse, and genetic hemochromatosis [35].

**Kidney Cancer**

Chronic arsenic exposure is capable of causing chronic renal insufficiency from cortical necrosis. Acute arsenic poisoning may cause acute tubular necrosis, with acute renal failure. Commonly being seen. Arsine gas and arsenic are known to cause tubular necrosis but arsine gas is more nephrotoxic. There is no strong evidence to prove that arsenic directly causes kidney cancer; however, a study of smelter workers in Tacoma, Washington (USA), showed a 30% increase in incidence of renal carcinoma in those who were chronically exposed to arsenic as a by-product of smelting non-ferrous metal ores. The mining workers and copper smelters also showed increased rates of lung cancer, gastrointestinal cancer, and hematolymphatic malignancies [25].

**Gastrointestinal Cancer**

Gastric carcinoma is the term for stomach cancer and adenocarcinoma is the most common form of cancer found in the gastrointestinal tract. Literature is replete with conflicting reports linking carcinoma of the gastrointestinal tract and arsenic ingestion. Observations were made mostly among factory workers who had developed multiple cancers many years after initial exposure. For example, a study of Swedish glass-blowers exposed to high consumption of lead, arsenic, antimony, and manganese revealed increased risk of death from cancer of the stomach, lung, and colon. Also, a study of 839 copper smelters in Japan found significant increase in mortalities from lung and colon cancers. In Ontario, Canada, excess mortality from stomach cancer was observed among gold miners.

**Brain Cancer**

The primary malignant brain tumor is referred to as glioma because it originates from the glial cells of the nervous system. In the brain, gliomas are commonly found in the cerebral hemispheres but other
areas may be affected including the optic nerve, the brain stem, and, particularly among children, the cerebellum. There exist different groups of gliomas based on the type of glial cell involved. Astrocytomas develop from astrocytes (star-shaped glial cells). Astrocytomas, the most common type of glioma, are also the most common type of primary brain tumor. Arsenic-exposed patients may develop destruction of axonal cylinders, leading to peripheral neuropathy [36].

**Arsenic and DNA damage**

The genetic basis of arsenic-induced mutagenesis and tumorigenesis may be attributed to direct free radical attack on DNA strands resulting in damage. Impairment of catalase and superoxide dismutase (SOD)-associated DNA breakage and apoptotic cell death were noticed in intestinal epithelial cells of rats chronically exposed to iAs. Hydrogen peroxide (H$_2$O$_2$) associated free radicals are implicated in the high rate of DNA fragmentation in rodent lymphocyte and liver tissues of catalase knockout mice. Electron spin resonance with the spin-trap agent detects the generation of the hydroxyl radical (·OH) via MMA (II) when H$_2$O$_2$ is present and it might thus be participating in the DNA damage mechanism. These findings clearly indicate the importance of catalase in cellular protection from reactive oxygen species (ROS)-related damage. Chronic arsenic exposure in rats also caused significant single-strand DNA damage in neuronal cell and lymphocytes as depicted by single cell comet assay. It is accelerated by an increased production of ROS. These results are of significance in suggesting that chronic arsenic exposure in humans may result in a significant DNA degradation pattern in a mixed white blood cell (WBC) population with significant decrease of several serum antioxidant components including uric acid. Chronic arsenic exposure also leads to ROS-mediated, mitochondrial-driven, and caspase-dependent apoptosis in hepatic cells with a significant increase in glutathione disulfide (GSSG) levels and a decrease in glutathione reductase activity. This suggests that oxidative stress-related mitochondrial instability is an important factor for arsenic-related apoptotic tissue degeneration [37]. Arsenic-induced increase in 8-OHdG, a modified DNA base as reported in several studies, suggests that oxidative DNA damage is a major cause of arsenic-related mutagenesis. MMA has also been reported to induce the preneoplastic lesions in rats via the production of ROS. Arsenic and chromium in drinking water promote tumorigenesis in a mouse colitis-associated colorectal cancer model via a ROS-mediated Wnt/β-catenin signaling pathway. Arsenic exposure increased nicotinaminde adenine dinucleotide phosphate-reduced, NADPH oxidase1 (NOX1) and the level of 8-OHdG suggesting ROS-related DNA damage. The depletion of antioxidant enzymes, such as SOD and catalase, has been shown and linked to arsenic-related DNA and tissue damage [7]. By decreasing the nullifications of superoxide anion radicals, leading to increased oxidative stress.

4. **Conclusion**

Geological factors constitute the primary sources of arsenic in groundwater, rendering many individuals in affected areas susceptible to arsenic poisoning due to the prolonged consumption of contaminated water. Recognizing the potential health risks, endeavors have been undertaken to tackle the issue. Arsenic exposure has been associated with the onset of diverse malignancies and solid tumors, including lung and bladder cancers. The mechanisms underlying arsenic-associated carcinogenesis seem to hinge on factors such as the intensity of exposure, genetic predisposition, and geographical location. Moreover, chronic conditions such as hypertension, cardiovascular disease, and diabetes have been noted in connection with arsenic exposure. Additionally, prolonged exposure to arsenic has been reported to induce long-term memory loss and disruptions in hormonal regulation.

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