European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Review Article

Chronic Arsenic Exposure from Groundwater and Long-Term Health Consequences

Article History:

Name of Author:
Nuralya Fazhana Azmina Noramizan[1], Nur Elliyana Elissa Muhammad Nazri[1], Nur Raihan Hanim Mohd[1], Nur Arissa Balqis Mohd Shairi[1], Puteri Nur Aryani Alia Roshidi[1], Muhammad Zulfiqah Sadikan[1*], Halilol Rahman Mohamad Khan[1]

Affiliation: *[1]Faculty of Pharmacy and Health Sciences, Universiti Kuala Lumpur Royal College of Medicine Perak, Jalan Greentown, Ipoh 30450, Perak, Malaysia*

Corresponding Author:
Muhammad Zulfiqah Sadikan

Received: 04-11-2025
Revised: 16-11-2025
Accepted: 16-12-2025
Published: 30-12-2025

Abstract: Arsenic contamination of groundwater represents one of the most pervasive and insidious environmental health threats worldwide, affecting more than 230 million people across over 100 countries. Chronic exposure to inorganic arsenic, primarily through drinking water, is strongly associated with multisystem toxicity, including dermatological lesions, cardiovascular disease, neurotoxicity, metabolic disorders, and increased risks of skin, lung, bladder, liver, and kidney cancers. This review synthesizes current evidence on the sources, chemical forms, molecular mechanisms, clinical manifestations, and management strategies of arsenic poisoning, with particular emphasis on groundwater-derived exposure. In groundwater systems, arsenic predominantly exists as trivalent arsenite (As^{3+}) and pentavalent arsenate (As^{5+}), with toxicity influenced by redox conditions, pH, and biological methylation. At the molecular level, arsenic disrupts cellular energy metabolism through phosphate mimicry, inhibition of mitochondrial enzymes, oxidative stress induction, and dysregulation of redox signaling pathways, including the Nrf2-Keap1 axis. Clinically, prolonged exposure results in progressive organ damage, neurocognitive impairment, and carcinogenesis, often manifesting after years of silent exposure. The review highlights Bangladesh as a major historical case study illustrating the scale and complexity of arsenic contamination driven largely by geogenic processes. Current management strategies encompass chelation therapy, nutritional interventions, and emerging bio-based and microbial remediation technologies, alongside conventional water treatment approaches. Despite advances, significant gaps remain in affordable remediation, long-term clinical management, and policy implementation, particularly in resource-limited settings. Addressing arsenic toxicity requires integrated, interdisciplinary strategies combining environmental monitoring, medical management, and public health interventions to reduce exposure and mitigate long-term health impacts.

Keywords: Arsenic poisoning; groundwater contamination; chronic arsenicosis; oxidative stress; mitochondrial dysfunction; neurotoxicity; carcinogenesis; water remediation; public health.

INTRODUCTION

Arsenic (As) contamination in groundwater poses a serious global health threat especially because groundwater is a major source of drinking water in many regions. Chronic exposure to As has been linked to carcinogenic, cardiovascular and neurological disorders, silently affecting over 230 million people worldwide (Shaji et al., 2021). When groundwater becomes contaminated, it serves as a way for As to enter the body through drinking water, leading to long term poisoning and chronic health issues (Hu et al., 2024; Sultan et al., 2025). The World Health Organization (WHO) identifies As contamination as a serious public health issue due to its widespread presence and the toxic nature of its inorganic forms. Long term exposure to arsenic is often unnoticed because its harmful effects develop gradually and quietly. Health problems like skin lesions, heart disease and cancers of the skin and internal organs usually appear only after years of exposure.

Chemically, arsenic is a metalloid with an atomic number of 33. In groundwater, it mainly exists in two inorganic oxidation states: trivalent arsenite (As^{3+},

commonly present as H_3AsO_3) and pentavalent arsenate (As^{5+}, typically found as $H_2AsO_4^-$ or $HAsO_4^{2-}$, depending on the pH). Among these, arsenite is the more toxic form. Elemental arsenic naturally occurs in minerals such as arsenopyrite (FeAsS) and can be released into groundwater through both natural (geogenic) and human (anthropogenic) processes (Sultan et al., 2025). The primary arsenic species contributing to water contamination are arsenite (H_3AsO_3) and arsenate (H_3AsO_4), with their distribution influenced by the pH and redox conditions of the aquifer.

Historically and globally, arsenic contamination of groundwater has caused one of the largest environmental poisoning incidents, with over 230 million people at risk globally, predominantly in Asia for example Bangladesh's 1990s crisis, India, Pakistan, China, Nepal, Vietnam, and Cambodia but also in parts of South America, Africa, and North America. Clinical manifestations of long-term exposure include arsenicosis which is a chronic condition with skin lesions such as hyperpigmentation, keratosis and elevated risks of skin, lung, bladder, kidney, and liver cancers (Mazumder, 2008). The World Health Organization (WHO) has set a guideline limit of 10 µg/L for arsenic in drinking water due to its carcinogenic and systemic health impacts (Frisbie & Mitchell, 2022).

Arsenic contamination is largely geogenic, arising from natural geological formations, particularly in unconsolidated sedimentary aquifers such as those in the Himalayan foothills and young orogenic belts, where tectonic activity promotes arsenic mobilization. Industrial operations, mining and the use of arsenic containing pesticides have worsened contamination levels (Medunić et al., 2019). In order to address this complex issue, it requires collaboration across scientific, engineering and policy disciplines to ensure effective monitoring, control and protection of vulnerable populations.

Literature Search Strategy

A comprehensive literature search was conducted to identify relevant peer-reviewed articles published between 2000 and 2025. Electronic databases including PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar were systematically searched. Key search terms and Boolean combinations included: "arsenic contamination", "groundwater arsenic", "chronic arsenic poisoning", "arsenicosis", "arsenic toxicity mechanisms", "oxidative stress", "mitochondrial dysfunction", "Nrf2 pathway", "arsenic neurotoxicity", "arsenic carcinogenesis", and "arsenic remediation technologies". Reference lists of relevant review articles and WHO reports were manually screened to identify additional studies. Inclusion criteria comprised original research articles, systematic reviews, meta-analyses, and authoritative reports focusing on human health effects, molecular mechanisms, epidemiology, and remediation strategies related to arsenic exposure. Non-English articles, conference abstracts without full text, and studies lacking relevance to groundwater-related arsenic exposure were excluded.

2. Mechanism of Toxicity

There are two major formulations of arsenic as far is concerned with exposure to human beings is concerned, which are pentavalent, arsenate (As^V), and trivalent, arsenite (As^{III}). These species have different chemical structures and redox potentials; hence, determining their immediate targets of the molecules, which is a result of the initiation of separate, but overlapping, toxicological cascades within the cell.

2.1 The Methylation Pathway

Biosphere inorganic arsenic on absorption is biotransformed, mostly in the liver, in a series of reducing and oxidative methylation involving enzymes such as arsenic methyltransferase (AS3MT). This route, which has been traditionally viewed as a detoxification route leading to the excretion of the urine, synthesizes a calcium that can be arranged as monomethylarsonic acid (MMA^V), monomethylarsonous acid (MMA^{III}), dimethylarsinic acid (DMA^V), and dimethylarsinous acid (DMA^{III}) (Olujimi Sadiku & Rodríguez-Seijo, 2022).

These metabolic intermediates define the basic toxicity profile of arsenic, not only based on the parent compound, but rather on these intermediate molecules. The trivalent methylated counterparts, namely MMA^{III} and DMA^{III}, are more chemically active than As^{III} (parent) (Bergquist et al., 2009) (Bergquist et al., 2008). MMA^{III} has been reported to be much stronger as an inhibitor of the essential cellular enzymes compared to inorganic arsenite (Leslie, 2012). Therefore, the biological action supposed to lead to detoxification is a biological paradox that converts into the temporary formation of highly cytotoxic intermediates. This observation underscores one very important feature of chronic arsenic toxicity. Individual differences in metabolic efficiency and resulting ratios of intermediate trivalent species produced would have a significant effect on arsenic disease predisposition.

2.2 Molecular Mechanisms of Cellular Energy and Metabolic Impairment

There are two major and mechanistically differentiated attacks that launch chronic arsenic toxicity. As^V and Phosphate mimicry with vicinal dithiols-trivalent arsenicals.

2.3 Phosphate Mimicry and Arsenolysis of Arsenate (As^V)

Pentavalent arsenate (As^V) ions are structural and

chemical analogous to inorganic phosphate (Pi). This homology is almost perfect and enables As^{V} to, in effect to replace Pi in many enzyme reactions carried out throughout the cell, mostly energy transfer (Silva et al., 2011). This is known as arsenolysis, and it has crippling effects on the production of ATP in cells. In major metabolic metabolites, namely those that are mediated by glyceraldehyde-3-phosphate dehydrogenase in glycolysis or during an oxidative phosphorylation response in the mitochondrion, As^{V} has been observed to replace Pi to a set of unstable arsenate ester intermediates. An example of research that attests this mechanism is that in the interaction with the inosine, arsenate, a ligand, it is positioned in an ancestral site of phosphate and locates to attack the C1 ribose (Tawfik & Viola, 2011). The corresponding arsenate anion, as opposed to stable phosphoanhydride interaction, is very unstable itself and quickly hydrolysed (Silva et al., 2011). This quick hydrolysis inhibits the development of stable and high-energy phosphate bonds. This process has been shown to be able to uncouple energy production with the electron transport chain, which decreases net ATP generation significantly but has no effect on or even accelerates oxygen consumption. The effects are a disastrous bioenergetic crisis, especially in tissues that have high metabolism rates.

2.4 Trivalent Arsenical Dithiol Inhibition of Mitochondrial Respiration

The affinity of trivalent arsenicals (As^{III}, MMA^{III}, and DMA^{III}) towards proximity -SH and -SH groups indicates affinity to vicinal -SH and -SH groups on a protein chain occurring closely. They bind covalently to these groups to become stable, five-membered rings, which are powerful enzyme inhibitors (Shen et al., 2013). This is inhibited in specific combinations of the mitochondrial complexes that use lipoic acid cofactor (Bergquist et al., 2009). The most common and most sensitive target of arsenical inhibition is arguably the pyruvate dehydrogenase (PDH) complex. PDH plays an essential role in the connection of glycolysis and the tricarboxylic acid (TCA) pathway through the pyruvate to Acetyl-CoA transformation (Kulshrestha et al., 2014). Arsenite and its methylated metabolites bind to the lipoic acid moiety directly, which changes its position and thus prevents the activity of PDH. This will clog the central metabolic center, dizzying the aerobic cellular respiration. In addition, MMA^{III} has also been proven to be a more effective inhibitor of PDH in comparison to inorganic arsenite (Olujimi Sadiku & Rodríguez-Seijo, 2022). There are other key mitochondrial complexes that are effectively inhibited such as including α-ketoglutarate dehydrogenase (KGDH) and Succinyl CoA synthase. Through these trivalent arsenicals, aggravating the imbalance of the TCA cycle. Mechanistic features present here are a considerable reliance on the redox state of the target enzyme to the inhibition. The reported cumulative inhibition of these complexes presupposes that the lipoic acid cofactor should be in the reduced dithiol form (Usacheva et al., 2022). This implies that the redox condition in the vicinity of the mitochondria determines the effectiveness of arsenic as an intoxicant. Throughout the initial inhibition of PDH and KGDH consume NADH and interfere with the electron transport chain, it quickly prefers a reduced state, thus accelerating the binding and compounding toxic effect. This causes energy shortage and dysfunctional cellular respiration and consequent cell death (Chalifoux et al., 2023).

2.5 Inhibition of Thioredoxin and Glutathione Systems

In addition to directly inhibiting the mitochondria, trivalent arsenicals have a significant adverse effect on the redox defence ability of the cell, as they attack key thiol-containing enzymes. MMA^{III} is an established strong inhibitor of Thioredoxin reductase (TrxR). The thioredoxin system (Trx/TrxR) plays a crucial role in cell proliferation and survival, and it has antiapoptotic effects. On the same note, MMA^{III} blocks Glutathione (GSH) reductase (Hwang et al., 2024). Blockage of this enzyme causes inhibition of the regeneration capacity of the cell, decreasing GSH, the major intracellular small molecule antioxidant. Co-inhibition of these redox maintenance systems causes extreme intracellular redox disequilibrium, overwhelming the cellular defence, causing cytotoxicity and death (Mao et al., 2025).

2.6 Mechanisms and Products of Reactive Oxygen Species Generation

The dysfunctional mitochondria are the main sources of the reactive oxygen species (ROS) in the toxicity of arsenic. Blockage of the mitochondrial catalases, including PDH and KGDH, empty the mitochondrial NADH pool and causes the release of electrons through the uncoupled electron transport chain (Prakash et al., 2022). Arsenic is also associated with the production of ROS due to redox cycling and strong binding of the sulfhydryl group. Prolonged exposure to arsenic triggers the formation of various ROS species such as superoxide (O_2^-). Hydrogen peroxide (H_2O_2) and the greatly devastating hydroxyl radical (OH^-). These superoxide radical species play a dual role. They are directly damaged by oxidation (Bonetto et al., 2014). They cause direct oxidative damage to essential biomolecules (lipids, proteins, and DNA), which induce dysfunction in cells and, at the same time, serve as messengers, can modify signal transduction pathways that control the expression and cell fate (Figure 1).

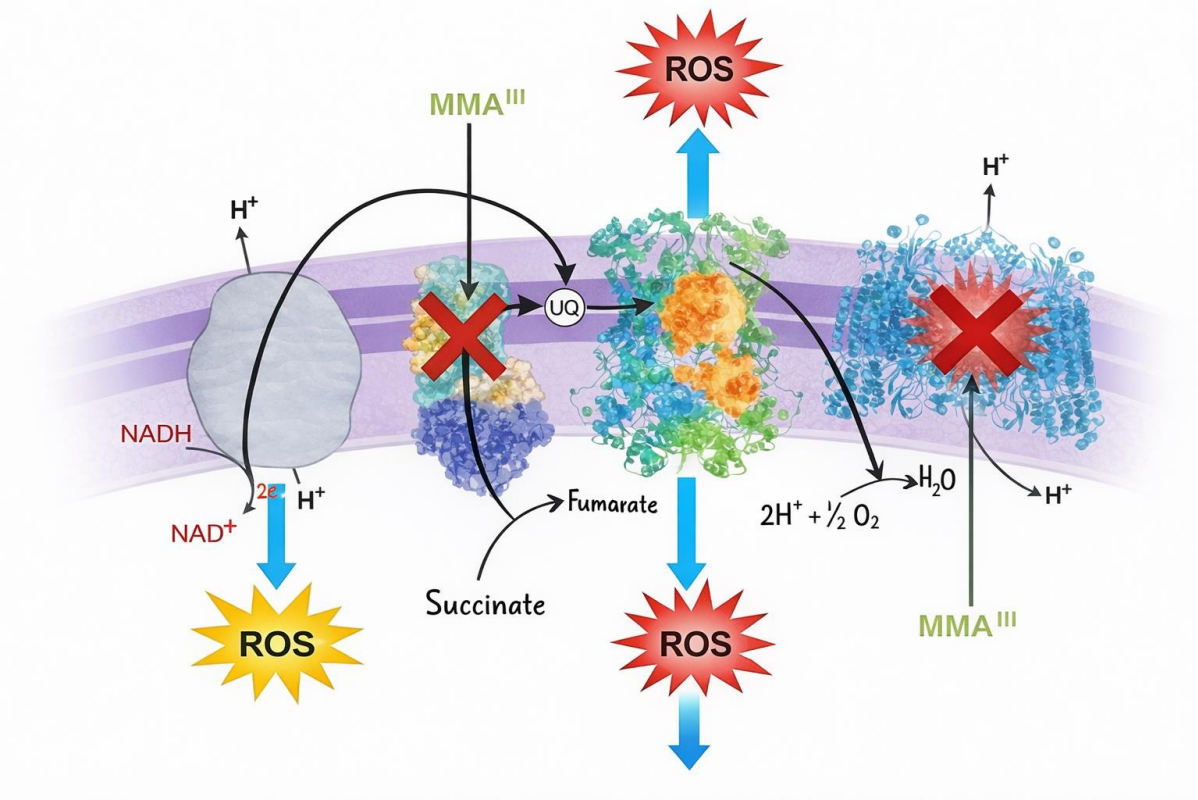


Figure 1. Proposed mechanism underlying the MMA^{III}-inhibited of the electron transfer chain (ETC) in mitochondria.

2.7 The Nrf2-Keap1-ARE Pathway Modulation

The primary defence mechanism that is active in the cell and responds to oxidative and electrophilic stress in the Nrf2-Keap1 pathway (Lau et al., 2013). Arsenic corrects the activity of this pathway in response to its generated ROS and through direct chemical interactions (Hu et al., 2020). During stressful conditions, ROS excess production leads to the canonical pathway, in which Keap1 releases Nrf2, and this enables the pathway to translocate to the nucleus. Nuclear-bound Nrf2 is next required to bind antioxidant response element (ARE) and enhance the expression of protective genes, including HO-1 and the NQO1 (Hu et al., 2020).

Noncanonical mechanisms of Nrf2 pathways have also been implicated in the activation of Nrf2 by arsenic. This involves a pathway that engages the scaffolding protein p62, in which the direct interaction of p62 inactivates Keap1 to stabilize Nrf2 protein and hence results in subsequent upregulation of the ARE-bearing gene transcription (Lau et al., 2013). This noncanonical activation pathway is noteworthy as it has been demonstrated that the deficiency of the necessary genes of autophagy results in the development of p62-positive aggregates. Failure to recycle efficiently the damaged cells, which have protective, high Nrf2-controlled defence protective capabilities. This pathway offers an important molecular connection between chronic exposure to arsenic and disordered cellular waste disposal and the eventual stimulation of tumor progression.

2.8 Modulation of Proliferative and Inflammatory Signalling Pathways

Arsenic substantially changes the signal transduction pathways using the generation of ROS or through reversible oxidation of protein sulfhydryl (-SH) residues, thereby activating or inhibiting diverse transcription factors and regulating gene expression (Hu et al., 2020). Some of the key pathways that are impaired are the mitogen-activated protein kinase (MAPKs) and the general tyrosine phosphorylation system. Increased ROS/ERK signaling has been associated with cell proliferation caused by arsenic. Arsenic promotes pro-survival signaling as well as inflammatory signaling. It induces dose-related production of ROS that results in the activation of activator protein-1 (AP-1). On the same note, NF-kB activation and the promotion of NF-kB signaling in response to arsenic exposure are possible (Hu et al., 2020). Simultaneous activation of AP-1 and NF-kB enhances chronic inflammation, cell survival, and apoptotic resistance, developing a microenvironment conducive to tumor growth to a large extent. The capability of trivalent arsenicals to react directly with thiols gives it the capability to function as a direct chemical switch, altering the activity of transcription factors via reversible oxidation of their -SH, without being anymore or less active in conjunction within generalized ROS stress (Shen et al., 2013).

2.9 Systemic Physiological Effects and Affected Organ Systems

2.9.1 Cardiovascular and Vascular System Pathophysiology

There is a strong correlation between chronic arsenic and cardiovascular risk, which are expressed through hypertension, atherosclerosis, and peripheral arterial disease (PAD). Blackfoot disease (BFD) is the extreme form of PAD, which was historically prevalent in some highly exposed groups and is also the consequence of high doses of arsenic in the long term (Tseng, 2005). The molecular pathophysiology behind these complications is vascular endothelial dysfunction (VED), which is frequently primary to the structural alterations and clinical manifestation (Farzan et al., 2022). Mechanistically, VED is caused by injury to the endothelium, dysfunctional vasoreactivity, and the essential depletion of the bioavailability of the powerful vasodilator, nitric oxide (NO). The cumulative impact of oxidative stress, as well as chronic inflammatory signaling by NF-kB and AP-1, is behind the dysfunction (Hu et al., 2020). Arsenic facilitates atherogenesis in several pathways, including causing endothelial cell damage, stimulating smooth muscle cell proliferation, and preserving elevated of oxidative stress (Farzan et al., 2022).

2.9.2 Neurotoxicity and Neurological Impairment

The brain is distinctively susceptible to arsenic toxicity because of its high metabolic rate and excessive sensitivity to oxidative stress. Arsenic exposure is documented to induce oxidative stress damage through the impaired antioxidant enzyme activities in the brain (Thakur et al., 2021). The primary cause of neurotoxicity due to arsenic is this augmented state of oxidative stress (Thakur et al., 2021).

2.9.3 Peripheral Neuropathy

Traditionally, arsenic disrupts the neuroskeletal integrity in its peripheral nervous system (Singh et al., 2011). The ensuing structural injury significantly reduces the nerve conduction velocity in the peripheral nerves, resulting in the clinical presentation of peripheral neuropathy. The active energy needs of nerve conduction imply that the mitochondrial poisoning (PDH/KGDH inhibition) contributes to this pathology.

2.9.4 Central Neurotoxicity and Cognitive Decline

Arsenic metabolites inhibit essential excitatory receptors in the central nervous system, and it has a direct effect on cognition. In particular, the exposure to arsenic and its products, including monomethylarsonous acid, kills NMDA receptors both in the hippocampus. Since NMDA receptors play a central role in synaptic plasticity, learning, and memory, suppression of these transporters is one of the important contributors to neurobehavioral disorders and cognitive dysfunction (Singh et al., 2011).

2.9.5 Disruption of Neutrophin signaling

The most targeted with arsenic-induced central neurotoxicity is the targeting of neuronal survival pathways. Arsenic actively interferes with neurotrophin signaling by inhibiting the phosphorylation of the TrkB receptor, known as Tropomyosin Receptor Kinase, in response to neurotrophins. TrkB is the receptor that performs this role of Brain-Derived Neurotrophic Factor (BDNF), which facilitates neuronal survival and prevents apoptosis (Pandey et al., 2017). TrkB inhibition is an effective way to close major downstream survival signaling, such as PI3K-AKT and ERK-CREB. This inhibition results in direct hippocampal neuronal apoptosis and debilitating cognitive issues (Pandey et al., 2017). Thus, arsenic can affect deep neurodegeneration in a two-pronged attack. First, random damage through mitochondrial ROS, and second, selective chemical inhibition of the initial intrinsic rescue and survival pathway.

3. Clinical and Health Effects

As noted by Demissie et al. (2024), arsenic is a highly dangerous carcinogen and is viewed as one of the most harmful endocrine disruptors. It poses various health risks. Both organic and inorganic forms of arsenic exist, and they affect human health in different ways. Inorganic arsenic is particularly troubling due to its toxic effects. People are exposed to it through contaminated drinking water and food sources (Bhat et al., 2024).

In general, signs of acute arsenic poisoning usually show up within thirty minutes after ingestion. However, these signs may be delayed if arsenic is consumed with food. The early symptoms of arsenic toxicity can include muscle aches, abdominal pain along with nausea, vomiting, and diarrhea, as well as skin flushing (Prakash & Verma, 2021). The immediate effects of acute arsenic poisoning may involve vomiting, abdominal discomfort, and diarrhea. Following these symptoms, individuals might experience numbness and tingling in their limbs, muscle cramps, and, in severe cases, possibly death .

Although signs and symptoms of chronic arsenic poisoning due to drinking groundwater do not usually appear until after a minimum of five years of consumption, the initial signs do tend to appear on the skin. According to the World Health Organization, early signs and symptoms that may occur with long-term exposure include changes in skin pigmentation and keratosis. Hyperpigmentation may manifest as spotty pigmentation, resembling raindrops, as

diffuse dark brown patches, or as a generalized darkening of the skin on the arms or trunk. Hyperpigmentation areas may be interspersed with small, rounded patches of hypopigmentation on the face, neck, and back.

Prakash et al. (2021) indicated that long-term consumption of inorganic arsenic may cause health effects impacting multiple systems, including skin, lung, liver, kidney and urinary bladder cancers. The International Agency for Research on Cancer classified arsenic and its compounds as carcinogenic to humans. It also outlined that exposure to arsenic in drinking water poses a cancer threat in people. Long-term exposure to inorganic arsenic may cause many health disorders, including developmental abnormalities, diabetes, respiratory and cardiovascular diseases. Myocardial infarction due to arsenic may cause high mortality rates. Prolonged exposure to arsenic during pregnancy may result in severe risks for pregnant mothers and their developing infants, which include miscarriage and stillbirth. Children are highly vulnerable to neurological conditions and have a higher infant mortality rate. It has also been observed in various studies that children are adversely impacted by arsenic exposure, affecting cognitive development, intelligence, and memory.

Arsenic in groundwater can cause chronic poisoning, which affects the body systems and numerous organs. Inorganic arsenic is transported in the blood and progressively accumulates in different tissues. The skin is often the first organ that displays visible signs of chronic exposure, normally in the form of areas of darkening, lightening of the skin, and thickened skin on the palms and soles. Prolonged exposure increases the risk for skin cancer through DNA damage and oxidative stress (Speer et al., 2023).

According to Fatoki and Badmus (2022), the liver is the main organ of the body that is affected by many toxic agents, due to its responsibility for detoxification and metabolic processing of xenobiotics. This is mainly due to the presence of xenobiotic-metabolizing enzymes within the cells of the liver. Ingestion of arsenic in low, moderate, or high amounts can lead to significant toxicity to the liver. It commonly accumulates within the liver tissue, leading to degeneration characterized by fatty liver, hepatocyte damage, and disturbed methylation processes, all of which collectively impair the detoxification capacity of the liver. Prolonged exposure can lead to the development of liver fibrosis and cancer. Prolonged exposure to sodium arsenate at different concentrations can alter the normal structure of the liver, cause cytoplasmic damage, collapse the central vein, and distend hepatic sinusoids, which are all signs of severe liver toxicity.

Another organ to consider is the kidneys. Although the major site of arsenic biotransformation is at the hepatocytes, renal cells are important for excretion of the toxin from the body (Prakash et al., 2021). There is an association of arsenic exposure from polluted drinking water and developement of renal dysfunction (Farkhondeh et al., 2021). The exposure has been associated with enhanced inflammatory responses and a decreased estimated glomerular filtration rate (eGFR). In addition, increased levels of plasma creatinine and urea have been identified, indicating a decline in kidney function. In particular, increased blood creatinine levels indicate decreased filtration ability, hence lower renal ability. This will lead to a renal function impaired state that provided chronic kidney disease due to cellular oxidative damage and inflammation within renal cells due (Fatoki et al., 2022).

Besides that, arsenic drastically affects the cardiovascular system, resulting in endothelial dysfunction, atherosclerosis, and hypertension through the mediation of increased oxidative stress, inflammation, and impairment of nitric oxide signalling (Figure 2). These changes increase the risk for ischemic heart disease and stroke (Frisbie et al., 2022). Neurologically, chronic arsenic exposure causes neurotoxic effects to the nervous system, which results in peripheral neuropathy, cognitive impairment, memory loss, and developmental impairment in children. These effects have been related to mitochondrial damage and diminished neurotransmitter activity.

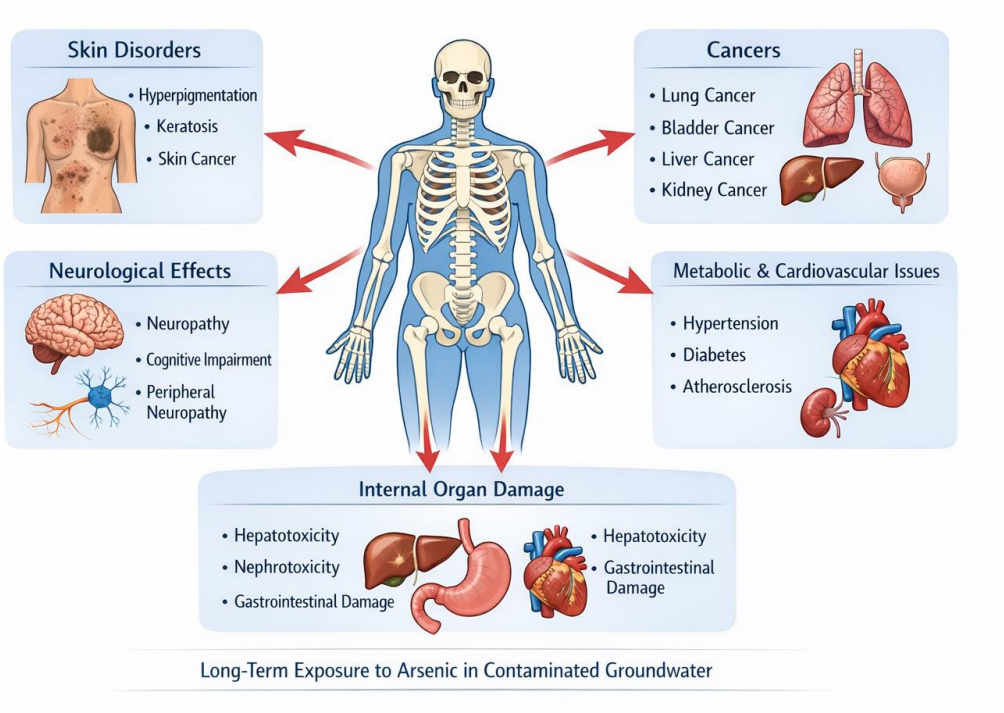


Figure 2: Clinical health effects associated with chronic arsenic exposure through contaminated groundwater.

4. Case Example of Historical Event

In 1993, Bangladesh was reported to be affected by groundwater contamination, and in 1994, the first official cases of arsenicosis were reported. Approximately 95% of the local population in Bangladesh relied on tubewell water, and more than 50 million people were consuming arsenic-contaminated water. The worst-affected areas were in the southeast region of Bangladesh, where more than 90% of the tubewells in some districts were contaminated (Rahman et al., 2015). According to reports, out of 64 districts, 61 contained arsenic levels exceeding the World Health Organization (WHO) guideline limit of 10 µg/l for potable water, affecting more than 85 million people. It was stated that shallow groundwater from sedimentary lacustrine aquifers typically contains high concentrations of arsenic, whereas deeper aquifers which is more than 300 m deep are considered safe (Shaji et al., 2021). Numerous health problems have occurred as a result of arsenic toxicity in Bangladesh.

The use of tubewells was first introduced as an intervention to address contamination in various surface water sources such as ponds and rivers, as well as subsurface sources like dug wells, which were microbially contaminated with pathogens such as *Vibrio cholera,* leading to diarrheal diseases .Tubewell water was considered safe from microbial contamination, and hundreds to thousands of tubewells were installed through personal, governmental and non-governmental organization (NGO) initiative. This intervention was initially a success in providing safe water sources. However, new problem later emerged, as it was discovered that the groundwater from many tubewells contained high concentrations of arsenic exceeding safe levels (Rahman et al., 2015).

The Bengal Basin, one of the largest sedimentary basins in the world. Arsenic is present in Bangladesh's tubewell water primarily due to the movement of sediments from the Himalayan belt, which contributed to the formation of the Bengal Basin, along with the influence of the Ganges-Brahmaputra-Meghna (GBM) river system, which also contributed to tectonic activity, climatic changes, and sea level fluctuations. The GBM river system played a major role in the buildup of the Bengal Fan, transporting large volume of sediments over thousands of years. These sediments contained various minerals, including arsenic, which were deposited in the delta during Holocene period. Although anthropogenic activities such as industrial pollution and the use of agrochemicals and wood preservatives may locally elevate arsenic levels, the widespread contamination in the Bengal Basin is predominantly geogenic in origin (Rahman et al., 2015).

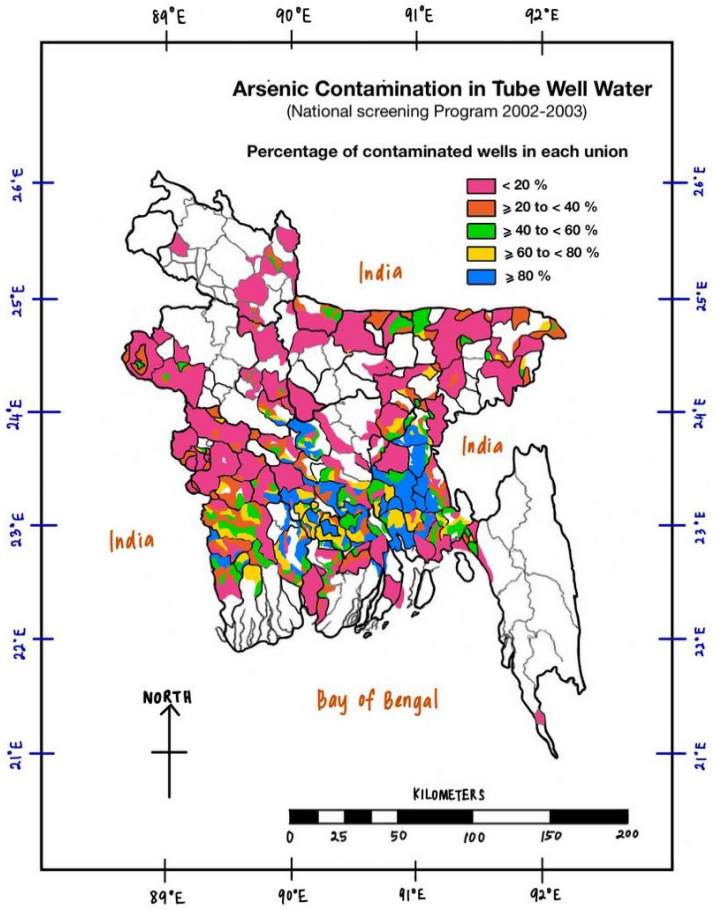


Figure 3. Arsenic contamination map of Bangladesh. This figure is adapted from (Ahmad et al., 2018)

Arsenic leaches into groundwater from GBM system through three identified mechanisms. First, the oxidation of arsenical pyrites in the alluvial sediments releases arsenic into the groundwater. This oxidation may occur when atmospheric oxygen enters the aquifers after large amounts of groundwater are pumped from shallow and deep tubewells. Second, microbes break down organic matter underground, creating oxygen-poor conditions. This causes iron compounds (FeOOH) to break down and releases the arsenic that placed them into the groundwater. Lastly, arsenic anions attached to aquifer minerals can be displaced into groundwater when phosphate ions compete for the same binding sites, resulting arsenic contamination in groundwater. Sources of phosphate include excessive use of phosphate fertilizers in agriculture, decomposition of buried peat, and other natural organic materials (Ahmad et al., 2018).

In 1983, the first patients with arsenic-related skin lesions were reported in West Bengal, and by 1987, similar cases were identified in neighbouring Bangladesh. The skin lesions showed pigmentation changes, mainly on the upper chest, arms, and legs, along with keratoses on palms of the hands and soles of the feet. Analysis of their water sources confirmed the diagnosis of arsenic-induced disease (Smith et al., 2000). Arsenic is a known carcinogen with the potential to cause cancers at multiple sites including in the skin, bladder, kidneys, prostate and lungs (Rahman et al., 2015). Over time, an increase in both skin and internal cancers was observed after a sufficient latency has been reached. Sustained consumption of drinking water containing 500 µg/l of arsenic may result in 1 in 10 people dying from arsenic-related cancers (Smith et al., 2000). Numerous other health problems associated with arsenic exposure have also been reported, ranging from dermatological signs such as melanosis, keratosis, and leukomelanosis to systemic effects including respiratory disorders, anaemia, weakness, conjunctival congestion, diabetes mellitus, hypertension, hepatopathy, peripheral neuropathy, non-pitting oedema of lower limbs, adverse reproductive outcomes, gangrene, Bowen's disease, cardiovascular and cerebrovascular diseases, peripheral vascular disease, and skin cancers, all of which are evident among the arsenic-exposed population in Bangladesh.

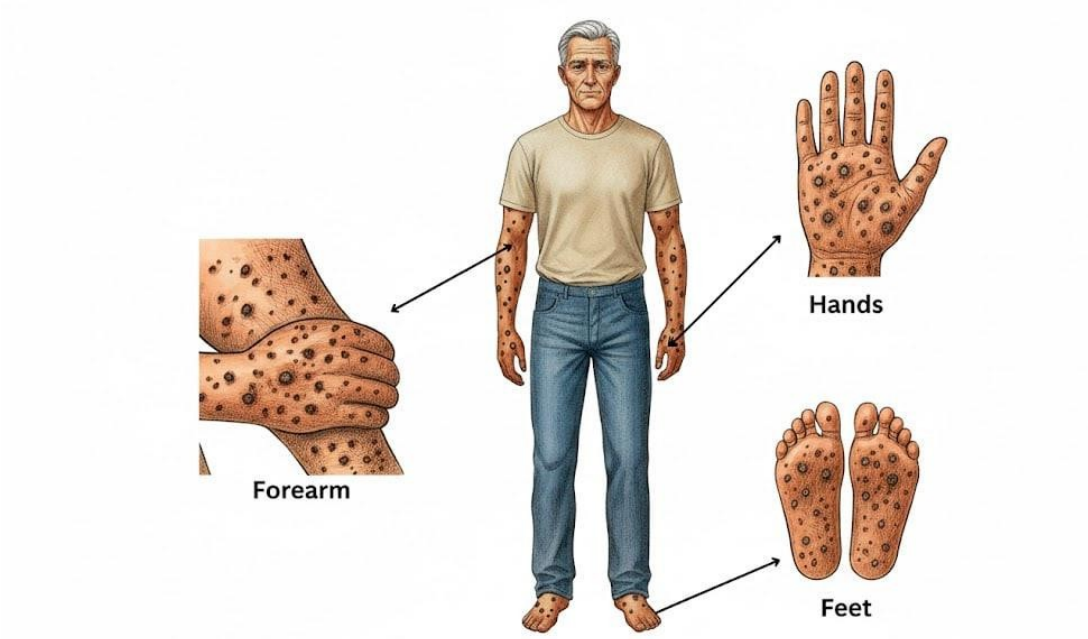
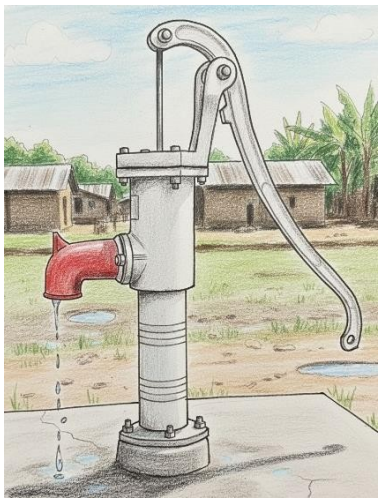
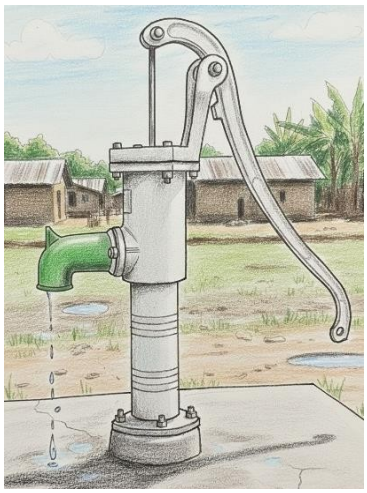


Figure 4. Effects of long-term exposure of humans to arsenic poisoning through drinking water and consumption of contaminated foods. These diseases are the direct evidence of human suffering resulting from arsenic contamination.

Several strategies have been introduced to reduce exposure to arsenic in drinking water sources. First, the identification and marking of tubewells with low arsenic content are essential to ensure the use of safe water. Second, household water filters, such as candle filtration systems, can serve as effective short-term alternatives because they are easy to maintain and promote good user compliance. Third, providing small packets of chemicals that can be mixed with water to remove arsenic offers a simple and inexpensive solution. When the treated water is left to stand overnight, arsenic is effectively reduced, and the method is easy to implement in rural settings. Forth, the use of treated surface water sources, such as ponds and rivers that have undergone filtration and chlorination, can also serve as an alternative supply. Fifth, highly contaminated wells should be closed once a temporary water source has been identified. Lastly, field test kits can be used to detect water samples containing arsenic concentrations of 100 mg/l or higher, although laboratory testing remains necessary to determine the exact concentration and ensure compliance with WHO standards (Smith et al., 2000).



(a) Red marked tubewell unfit for drinking



(b) Green marked tubewell fit for drinking

Figure 5. Screening of tubewells in Southwestern Bangladesh.

Arsenic contamination in groundwater has become major issue, especially in drinking water sources. Therefore, all

groundwater sources should be tested for arsenic contamination. Globally, around 107 countries are affected by arsenic by this problem. From these experiences, several important lessons have been learned regarding water management, the importance of safe water sources, and the need for compliance with water quality standards. The first lesson is the importance of collaboration with hydrogeologists to identify arsenic safe groundwater sources for water supply. Arsenic exposure reduction has been achieved through mapping the low arsenic groundwater zones for safer use. However, these zones are vulnerable to contamination if overpumped for irrigation or excessive supply. Regular monitoring is also essential, as studies show large scale groundwater extraction can alter flow patterns and increase arsenic levels. The second lesson is the use of field test kits to enable testing in rural and low-income areas. It is crucial to follow strict sampling protocols, including blanks, replicates, and quality assurance or quality assurance samples, to prevent contamination and minimize human error. The last lesson learned is the smaller water supply systems tend to have higher failure rates in arsenic treatment. The US EPA has demonstrated several effective arsenic removal technologies, such as coagulation or filtration, adsorptive media, ion exchange, and iron removal systems in order to help water utilities reduce arsenic levels to below 10 μg/L (Chwirka et al., 2004).

5. Management and Treatment

Category	Sub-category	Description	Strengths	Limitations	Source(s)
Medical Management	Chelation Therapy	BAL (dimercaprol), DMSA, DMPS used to bind inorganic and promote urinary excretion.	Effective for acute or moderate arsenic intoxication; reduces systemic load.	Limited efficacy in chronic exposure; potential adverse effects; requires medical supervisions.	(Balali-Mood et al., 2025; Bjørklund et al., 2020; Kuivenhoven & Mason, 2023)
	Supportive Care	Symptomatic treatment, hydration, correction of electrolyte imbalances, treatment of neuropathy, dermatologic lesions.	Essential for chronic arsenicosis; improves overall recovery and well-being.	Does not remove arsenic from the body; long-term management required.	(Kuivenhoven & Mason, 2023)
	Nutritional Rehabilitation	Supplementation with vitamins, minerals, antioxidants to reduce oxidative stress.	Improves antioxidant status; enhances natural detoxification pathways.	Adjunctive only; cannot reverse high cumulative arsenic burden.	(Arati et al., 2024; Bjørklund et al., 2022)
	Natural Protective Compounds	Plant-derivative polyphenols, flavonoids, antioxidants with detoxifying and anti-oxidative properties.	Low toxicity; offers additional protection; accessible in low-income settings.	Evidence mainly from preclinical studies; variable potency.	(Bjørklund et al., 2022)
Environmental Management	Conventional Water Treatment Technologies	Adsorption, ion exchange, membrane filtration.	Proven effectiveness; widely used globally.	High operational cost; maintenance challenges; not ideal for low-income regions.	(Mahamallik & Swain, 2023; Patel et al., 2023)
	Bio-based Remediation Technologies	Use of biological systems (plants, microbes) to remove arsenic.	Low cost, environmentally friendly, scalable.	Efficiency varies with environmental conditions; slower than conventional methods.	(Li et al., 2025; Rahman, 2025)

	Microbial / Biomineralization Approaches	Iron & manganese oxidizing microbes promote co-precipitation of arsenic via biomineralization (Figure 6).	Highly sustainable; efficient in reducing groundwater arsenic; minimal chemical input.	Requires controlled conditions; long-term monitoring needed.	(Li et al., 2025)
	Regulatory & Public Health Measures	Monitoring groundwater, enforcing water quality standards, installing treatment plants, community education.	Large-scale, population-level protection; breaks exposure cycle.	Requires funding, infrastructure, political will.	(Kuivenhoven & Mason, 2023)
Integrated Management Approach	Technological + Medical + Nutritional Strategy	Combines environmental remediation with chelation, supportive care, and nutrition.	Holistic, sustainable, addresses both exposure and health outcomes.	Complex implementation; requires interdisciplinary coordination.	(Kuivenhoven & Mason, 2023)

Table 1. Integrated Clinical and Environmental Approaches for Arsenic Toxicity Management

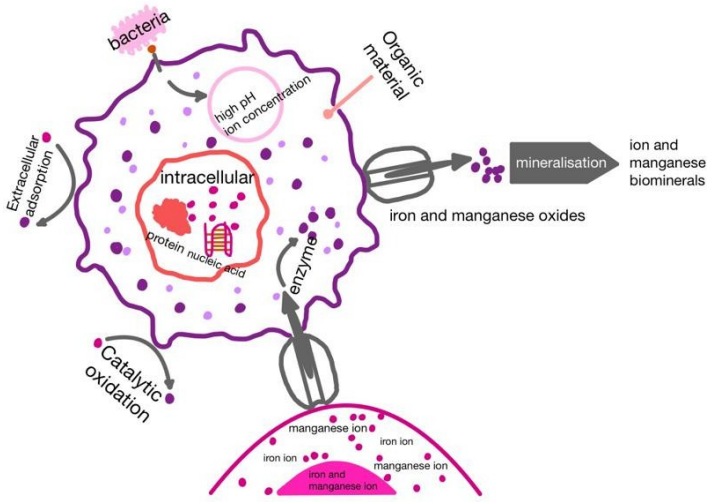


Figure 6. Biomineralization mechanism and microbial action of iron and manganese.

6. Current Issues and Gaps

Despite ongoing advancements, several critical issues and research gaps persist in the global management of arsenic poisoning. The long-term crisis of chronic arsenic exposure is increasingly complicated by emerging environmental dynamics, transforming it from a static geochemical problem into a dynamic, climate-driven challenge. Climate change and human activities continue to exacerbate arsenic mobilisation in groundwater, particularly in alluvial plains and deltaic regions, where fluctuating water tables accelerate leaching from sediments (Cao et al., 2025). Many existing remediation systems are costly, technically demanding, and unsuitable for rural or resource-limited communities, where the majority of affected populations reside (Mahamallik & Swain, 2023). Furthermore, although bio-based and microbial remediation technologies show considerable promise, their scalability and long-term field performance remain uncertain (Rahman, 2025).

From a clinical perspective, despite the availability of chelating agents such DMPS and DMSA, which are used for severe acute and some chronic cases, their limited efficacy against long-term morbidity underscores the need for continued research into more effective agents (Nurchi et al., 2020). Current research efforts focus on developing novel thiol and selenol-based compounds with improved therapeutic indices designed to more effectively mobilize and excrete arsenic following prolonged, low-level exposure (Bjørklund et al., 2022).

Another major concern is the bioaccumulation and persistence of arsenic in ecosystems. Contaminated plants, fish, and other food sources can serve as secondary exposure routes, perpetuating chronic poisoning even after improvements in water quality (Patel et al., 2023). Moreover, limited public awareness, inadequate policy enforcement, and the lack of affordable testing facilities continue to hinder early detection and mitigation efforts in developing regions (Kuivenhoven & Mason, 2023). Addressing these gaps requires integrated, community-based interventions that combine environmental monitoring, sustainable remediation technologies, and public health education to reduce arsenic exposure and mitigate its long-term health impacts globally.

CONCLUSIONS & PUBLIC HEALTH RELEVANCE

Over 230 million people in more than 100 countries are impacted by arsenic pollution in groundwater, which continues to be one of the most widespread and silent environmental health risks in the world. Numerous systemic consequences such as skin lesions, cardiovascular illness, liver and renal dysfunction, neurotoxicity and an elevated risk of various malignancies have been associated with chronic exposure to inorganic arsenic especially through drinking water (Shaji et al., 2021; Smith et al., 2018). The molecular basis of arsenic toxicity is the disruption of signal transduction, oxidative phosphorylation and cellular respiration which results in genomic instability, oxidative stress and mitochondrial dysfunction. The variety of long-term clinical symptoms seen in impacted populations can be explained by these mechanisms.

When geogenic contaminants are disregarded, groundwater meant to prevent microbiological infections might unintentionally result in chronic hazardous exposure as demonstrated by the global experiences especially in Bangladesh and West Bengal, India (Rahman et al., 2021). This emphasizes the necessity of enhancing risk communication, routine water testing and hydrogeological surveillance. Due to a lack of testing facilities and financial limitations, many rural areas are still struggle to meet the World Health Organization's (WHO) recommended limit of 10 μg/L for arsenic in drinking water.

From a clinical and policy standpoint, arsenicosis is a complicated socio-environmental problem that calls for interdisciplinary treatment rather than just being a medical illness. Its effects can be lessened by early diagnosis, community education, environmentally friendly water filtration systems and dietary therapies such as folate and selenium supplements. To guarantee that everyone has access to clean drinking water, public health policy should incorporate environmental monitoring, remedial initiatives and international cooperation.

In conclusion, arsenic in groundwater poses a persistent but avoidable threat to global health. Innovation in science, political dedication and social consciousness are necessary to address this challenge. In order to preserve the universal right to clean and safe water, it is both a scientific need and a humanitarian obligation to protect vulnerable communities against chronic arsenic poisoning (Shaji et al., 2021).

ABBREVIATIONS

As, arsenic; AsIII, trivalent arsenic or arsenite; AsV, pentavalent arsenic or arsenate; MMA, monomethylarsonic acid; MMAIII, monomethylarsonous acid; MMAV, pentavalent monomethylarsonic acid; DMA, dimethylarsinic acid; DMAIII, dimethylarsinous acid; DMAV, pentavalent dimethylarsinic acid; AS3MT, arsenic (+3 oxidation state) methyltransferase; Pi, inorganic phosphate; ATP, adenosine triphosphate; NADH, reduced nicotinamide adenine dinucleotide; PDH, pyruvate dehydrogenase; KGDH, α-ketoglutarate dehydrogenase; TCA, tricarboxylic acid cycle; ETC, electron transport chain; ROS, reactive oxygen species; O_2^-, superoxide anion; H_2O_2, hydrogen peroxide; OH-, hydroxyl radical; GSH, glutathione; Trx, thioredoxin; TrxR, thioredoxin reductase; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; ARE, antioxidant response element; HO-1, heme oxygenase-1; NQO1, NAD(P)H quinone oxidoreductase 1; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; AP-1, activator protein-1; NF-κB, nuclear factor kappa B; NO, nitric oxide; VED, vascular endothelial dysfunction; PAD, peripheral arterial disease; BFD, Blackfoot disease; NMDA, N-methyl-D-aspartate; TrkB, tropomyosin receptor kinase B; BDNF, brain-derived neurotrophic factor; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; CREB, cAMP response element-binding protein; WHO, World Health Organization; GBM, Ganges-Brahmaputra-Meghna; NGO, non-governmental organization; eGFR, estimated glomerular filtration rate; BAL, British anti-Lewisite (dimercaprol); DMSA, dimercaptosuccinic acid; DMPS, 2,3-dimercapto-1-propanesulfonic acid; US EPA, United States Environmental Protection Agency.

ETHICAL STATEMENT

This study does not involve any human or animal trials and no ethical approval required.

DATA AVAILABILITY

All data underlying this review are available within the cited literature.

FUNDING

This research was generously supported by a Short-Term Research Grant Scheme (UniKL/CoRI/str23038) from Universiti Kuala Lumpur (UniKL).

ACKNOWLEDGEMENT

The authors would like to thank Universiti Kuala Lumpur for supporting this study.

CONFLICTS OF INTEREST

Authors declare none.

REFERENCES

1. Ahmad, S. A., Khan, M. H., & Haque, M. (2018). Arsenic contamination in groundwater in Bangladesh: implications and challenges for healthcare policy. *Risk management and healthcare policy*, 251–261.
2. Arati, C., Chiranjeeb, R., Shruti, M. S., Mimangsha, C. D., Abdelgani-Baraka, G. A., Andy, L.,...Roy, V. K. (2024). Insights on the assessment of the potential of phytochemical chelating, protective, and detoxifying properties in managing chronic arsenic toxicity. *Indian Journal of Biochemistry and Biophysics (IJBB)*, *61*(7), 387–400.
3. Balali-Mood, M., Eizadi-Mood, N., Hassanian-Moghaddam, H., Etemad, L., Moshiri, M., Vahabzadeh, M., & Sadeghi, M. (2025). Recent advances in the clinical management of intoxication by five heavy metals: Mercury, lead, chromium, cadmium and arsenic. *Heliyon*, *11*(4).
4. Bergquist, E. R., Fischer, R. J., Sugden, K. D., & Martin, B. D. (2009). Inhibition by methylated organoarsenicals of the respiratory 2-oxo-acid dehydrogenases. *Journal of organometallic chemistry*, *694*(6), 973–980.
5. Bhat, A., Ravi, K., Tian, F., & Singh, B. (2024). Arsenic contamination needs serious attention: an opinion and global scenario. *Pollutants*, *4*(2), 196–211.
6. Bjørklund, G., Oliinyk, P., Lysiuk, R., Rahaman, M. S., Antonyak, H., Lozynska, I.,...Peana, M. (2020). Arsenic intoxication: general aspects and chelating agents. *Archives of toxicology*, *94*(6), 1879–1897.
7. Bjørklund, G., Rahaman, M. S., Shanaida, M., Lysiuk, R., Oliynyk, P., Lenchyk, L.,...Peana, M. (2022). Natural dietary compounds in the treatment of arsenic toxicity. *Molecules*, *27*(15), 4871.
8. Bonetto, J. G., Villaamil Lepori, E. C., & Puntarulo, S. Á. (2014). Update on the oxidative stress associated with arsenic exposure.
9. Cao, W., Fu, Y., Ren, Y., Li, X., Wang, Y., & Song, L. (2025). Arsenic health risk in shallow groundwater of the alluvial plains in the lower Yellow River, China: driving mechanisms of climate change and human activities. *Environment International*, 109711.
10. Chalifoux, O., Faerman, B., & Mailloux, R. J. (2023). Mitochondrial hydrogen peroxide production by pyruvate dehydrogenase and α-ketoglutarate dehydrogenase in oxidative eustress and oxidative distress. *Journal of Biological Chemistry*, *299*(12), 105399.
11. Chwirka, J. D., Colvin, C., Gomez, J. D., & Mueller, P. A. (2004). Arsenic removal from drinking water using the coagulation/microfiltratin process. *Journal-American Water Works Association*, *96*(3), 106–114.
12. Demissie, S., Mekonen, S., Awoke, T., & Mengistie, B. (2024). Assessing acute and chronic risks of human exposure to arsenic: A cross-sectional study in ethiopia employing body biomarkers. *Environmental Health Insights*, *18*, 11786302241257365.
13. Farkhondeh, T., Naseri, K., Esform, A., Aramjoo, H., & Naghizadeh, A. (2021). Drinking water heavy metal toxicity and chronic kidney diseases: a systematic review. *Reviews on Environmental Health*, *36*(3), 359–366.
14. Farzan, S. F., Eunus, H. M., Haque, S. E., Sarwar, G., Hasan, A. R., Wu, F.,...Jasmine, F. (2022). Arsenic exposure from drinking water and endothelial dysfunction in Bangladeshi adolescents. *Environmental Research*, *208*, 112697.
15. Fatoki, J. O., & Badmus, J. A. (2022). Arsenic as an environmental and human health antagonist: A review of its toxicity and disease initiation. *Journal of Hazardous Materials Advances*, *5*, 100052.
16. Frisbie, S. H., & Mitchell, E. J. (2022). Arsenic in drinking water: An analysis of global drinking water regulations and recommendations for updates to protect public health. *PLoS One*, *17*(4), e0263505.
17. Hu, K., Islam, M. A., Parvez, F., Bhattacharya, P., & Khan, K. M. (2024). Chronic exposure of arsenic among children in Asia: A current opinion based on epidemiological evidence. *Current opinion in environmental science & health*, *39*, 100558.
18. Hu, Y., Li, J., Lou, B., Wu, R., Wang, G., Lu, C.,...Xu, Y. (2020). The role of reactive oxygen species in arsenic toxicity. *Biomolecules*, *10*(2), 240.
19. Hwang, J.-h., An, G. J., Kim, C.-H., Chung, H. Y., & Lim, K.-m. (2024). Trivalent arsenicals induce skin toxicity through thiol depletion. *Toxicology and Applied Pharmacology*, *492*, 117115.

20. Kuivenhoven, M., & Mason, K. (2023). Arsenic toxicity. In *StatPearls [Internet]*. StatPearls Publishing.
21. Kulshrestha, A., Jarouliya, U., Prasad, G., Flora, S., & Bisen, P. S. (2014). Arsenic-induced abnormalities in glucose metabolism: Biochemical basis and potential therapeutic and nutritional interventions. *World Journal of Translational Medicine*, *3*(2), 96–111.
22. Lau, A., Zheng, Y., Tao, S., Wang, H., Whitman, S. A., White, E., & Zhang, D. D. (2013). Arsenic inhibits autophagic flux, activating the Nrf2-Keap1 pathway in a p62-dependent manner. *Molecular and cellular biology*, *33*(12), 2436–2446.
23. Leslie, E. M. (2012). Arsenic–glutathione conjugate transport by the human multidrug resistance proteins (MRPs/ABCCs). *Journal of Inorganic Biochemistry*, *108*, 141–149.
24. Li, F., Cai, J., Zhao, X., Liu, H., Ju, F., & Li, Y. (2025). Research Progress in the Remediation of Arsenic-and Cadmium-Contaminated Groundwater Mediated by Iron and Manganese Biomineralization. *Catalysts*, *15*(6), 570.
25. Mahamallik, P., & Swain, R. (2023). A mini-review on arsenic remediation techniques from water and future trends. *Water Science & Technology*, *87*(12), 3108–3123.
26. Mao, C., Jiang, D., Koong, A. C., & Gan, B. (2025). Exploiting metabolic cell death for cancer therapy. *Nature Reviews Cancer*, 1–19.
27. Mazumder, D. G. (2008). Chronic arsenic toxicity & human health. *Indian Journal of Medical Research*, *128*(4), 436–447.
28. Medunić, G., Fiket, Ž., & Ivanić, M. (2019). Arsenic contamination status in Europe, Australia, and other parts of the world. In *Arsenic in drinking water and food* (pp. 183–233). Springer.
29. Nurchi, V. M., Buha Djordjevic, A., Crisponi, G., Alexander, J., Bjørklund, G., & Aaseth, J. (2020). Arsenic toxicity: molecular targets and therapeutic agents. *Biomolecules*, *10*(2), 235.
30. Olujimi Sadiku, O., & Rodríguez-Seijo, A. (2022). Metabolič̌ki i genski poremeć́aji–pregled mehanizama toksič̌nosti i genotoksič̌nosti arsena i olova. *Arhiv za higijenu rada i toksikologiju*, *73*(4), 244–255.
31. Pandey, R., Rai, V., Mishra, J., Mandrah, K., Kumar Roy, S., & Bandyopadhyay, S. (2017). From the cover: arsenic induces hippocampal neuronal apoptosis and cognitive impairments via an up-regulated BMP2/Smad-dependent reduced BDNF/TrkB signaling in rats. *Toxicological Sciences*, *159*(1), 137–158.
32. Patel, K. S., Pandey, P. K., Martín-Ramos, P., Corns, W. T., Varol, S., Bhattacharya, P., & Zhu, Y. (2023). A review on arsenic in the environment: bio-accumulation, remediation, and disposal. *RSC advances*, *13*(22), 14914–14929.
33. Prakash, C., Chhikara, S., & Kumar, V. (2022). Mitochondrial dysfunction in arsenic-induced hepatotoxicity: pathogenic and therapeutic implications. *Biological Trace Element Research*, *200*(1), 261–270.
34. Prakash, S., & Verma, A. K. (2021). Arsenic: it's toxicity and impact on human health. *International Journal of Biological Innovations, IJBI*, *3*(1), 38–47.
35. Rahman, A. (2025). Integrated Approaches of Arsenic Remediation from Wastewater: A Comprehensive Review of Microbial, Bio-Based, and Advanced Technologies. *Toxics*, *13*(9), 768.
36. Rahman, B., Abir, T., Hossain, A. A., Islam, M. R., & Milton, A. H. (2015). The Association between Chronic Arsenic Exposure and Type 2 Diabetes: A Meta-Analysis. In *Handbook of arsenic toxicology* (pp. 557–573). Elsevier.
37. Shaji, E., Santosh, M., Sarath, K., Prakash, P., Deepchand, V., & Divya, B. (2021). Arsenic contamination of groundwater: A global synopsis with focus on the Indian Peninsula. *Geoscience frontiers*, *12*(3), 101079.
38. Shen, S., Li, X.-F., Cullen, W. R., Weinfeld, M., & Le, X. C. (2013). Arsenic binding to proteins. *Chemical reviews*, *113*(10), 7769–7792.
39. Silva, R. G., Hirschi, J. S., Ghanem, M., Murkin, A. S., & Schramm, V. L. (2011). Arsenate and phosphate as nucleophiles at the transition states of human purine nucleoside phosphorylase. *Biochemistry*, *50*(13), 2701–2709.
40. Singh, A. P., Goel, R. K., & Kaur, T. (2011). Mechanisms pertaining to arsenic toxicity. *Toxicology international*, *18*(2), 87.
41. Smith, A. H., Lingas, E. O., & Rahman, M. (2000). Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. *Bulletin of the world health organization*, *78*(9), 1093–1103.
42. Speer, R. M., Zhou, X., Volk, L. B., Liu, K. J., & Hudson, L. G. (2023). Arsenic and cancer: Evidence and mechanisms. In *Advances in pharmacology* (Vol. 96, pp. 151–202). Elsevier.
43. Sultan, M. W., Qureshi, F., Ahmed, S., Kamyab, H., Rajendran, S., Ibrahim, H., & Yusuf, M. (2025). A comprehensive review on arsenic contamination in groundwater: Sources, detection, mitigation strategies and

cost analysis. *Environmental Research*, *265*, 120457.

44. Tawfik, D. S., & Viola, R. E. (2011). Arsenate replacing phosphate: alternative life chemistries and ion promiscuity. *Biochemistry*, *50*(7), 1128–1134.
45. Thakur, M., Rachamalla, M., Niyogi, S., Datusalia, A. K., & Flora, S. J. S. (2021). Molecular mechanism of arsenic-induced neurotoxicity including neuronal dysfunctions. *International Journal of Molecular Sciences*, *22*(18), 10077.
46. Tseng, C.-H. (2005). Blackfoot disease and arsenic: a never-ending story. *Journal of environmental science and health*, *23*(1), 55–74.
47. Usacheva, A., Chernikov, A., Karmanova, E., & Bruskov, V. (2022). Pharmacological aspects of the use of lipoic acid. *Pharmaceutical Chemistry Journal*, *55*(11), 1138–1146.

