



## Review Article

## Arsenic exposure and its toxicity

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## ABSTRACT

Arsenic is a pollutant in the environment, and its poisoning of drinking water is considered a severe global health issue. Chronic arsenic exposure is linked to an increased risk of a variety of diseases, including cardiovascular abnormalities, diabetes mellitus, neurotoxicity, and nephrotoxicity. Furthermore, arsenic exposure has been linked to changes in liver function and the development of hepatotoxicity. Furthermore, only a few studies have shown that persistent exposure to arsenic causes carcinogenesis, particularly cancers of the skin, bladder, and lungs. The current study looks at a variety of processes that play a role in arsenic-induced toxicity and end-organ damage.

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## 1. Introduction

Arsenic is a naturally occurring metalloid, which means it has both metal and non-metal properties; it is commonly referred to as a heavy metal. Arsenic comes in a variety of forms known as allotropes. It is found in more than 245 minerals and is the twentieth most abundant element in the earth's crust. Human health is endangered by the inorganic forms, which mostly consist of arsenite (AsIII) and arsenate (As V) chemicals. Grey arsenic is the most common and widely used of the three arsenic allotropes, which include metallic grey, yellow, and black arsenic. Arsenic is a common element that may be found in the earth's crust, saltwater, and the human body. It ranks 20th in abundance in the earth's crust, 14th in seawater, and 12th in the human body. It makes up around five hundredths of one percent (0.00005 percent) of the earth's crust. It is found in nature in the form of metalloids or chemical compounds, and is primarily found in inorganic forms. It is divided into two species: arsenate and arsenite. Arsenite is far more

flammable, soluble, and mobile than As (V).<sup>1</sup>

## 1.1. Occurrence

Arsenic is found in the range of 1.5–3 mg kg<sup>-1</sup> in the environment. Arsenic is found in the environment as a result of both natural and man made sources. Arsenic is a naturally occurring element present in the earth's crust, soil and sediment, water, air, and plants and animals. Some agricultural and industrial sources might also discharge it into the environment. Arsenite concentrations in drinking water range from 0.01 to 3.7 mg/l (1.3–49 M). According to anthropogenic sources, arsenic can be obtained through man-made sources in a variety of products, with China, the Soviet Union, France, Mexico, Germany, Peru, Namibia, Sweden, and the United States accounting for about 90% of global production. According to WHO recommendations, arsenic has a safety limit of 10 g/l and a maximum acceptable value of 50 g/l in drinking water.<sup>2</sup>

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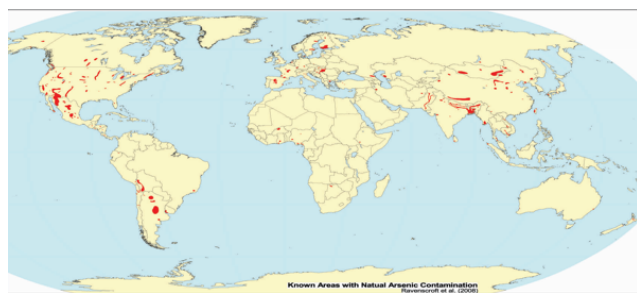


Fig. 1: Areas with arsenic contamination<sup>2</sup>

### 1.2. Uses of arsenic

Insecticides and pesticides containing arsenic were widely utilised over the world. Sodium arsenite and other inorganic arsenic compounds have traditionally been employed as non-selective soil sterilants to destroy weeds. Arsenic is also employed as desiccants and wood preservatives, in addition to insecticides and herbicides.<sup>3,4</sup> Arsenic compounds are also utilised to treat a variety of ailments. Arsenic has a long history of being used by peasants for skin cleanliness, suppleness, and other cosmetic advantages. It was also used to help those with breathing problems.<sup>5,6</sup> Fowler's solution (potassium arsenite), Donovan's solution (arsenic and mercuric iodides), Asiatic pills (arsenic trioxide and black pepper), de Valagin's solution (liquor arsenii chloridi), sodium cacodylate, arsphenamine (Salvarsan), neoarsphenamine, oxophenarsine hydrochloride (Mapharsen), arsthinol (Balarsen), acetarsone, tryparsamide and carbarsone are the most common medicinal preparations containing arsenic. References.<sup>7,8</sup> Despite the fact that it is only used for a few medical purposes, Arsenic is a well-known toxin that has a number of negative effects on physical and mental health.<sup>9</sup>

### 1.3. Exposure

Arsenic is a potent toxicant, and its abundance in many natural forms makes it quite frequent to be exposed to it. As a result, the opportunity for arsenic toxicity research is immense. Arsenic is typically absorbed by eating and inhalation. Another secondary way of exposure is through the skin, or dermal exposure. Humans can be exposed to arsenic through ingesting arsenic-laced food or drinking arsenic-laced water. Inhalation exposure can also occur through emissions from arsenic-containing fossil fuels, cotton gins, glass manufacturing operations, pesticide production facilities, smelters, and cigarette smoke. When working with preserved wood that has been treated with arsenic compounds, it is possible to get arsenic poisoning through the skin.<sup>10</sup>

### 1.4. Arsenic toxicity

Arsenic toxicity in the body depends on its chemical forms and oxidative stress as well as the physical state, absorption rate into the cells and its elimination rate, the nature of chemical substituents in toxic compounds, etc. A number of studies have shown that when compared among the inorganic arsenic compounds and organic arsenic compounds, the inorganic ones are more toxic and the inorganic AsIII is more toxic than inorganic AsV.<sup>11</sup> The toxicity order of arsenic compounds may be depicted as Arsines > iAsIII > arsenoxides(org AsIII) > iAsV > arsonium compounds > As<sup>12,13</sup>

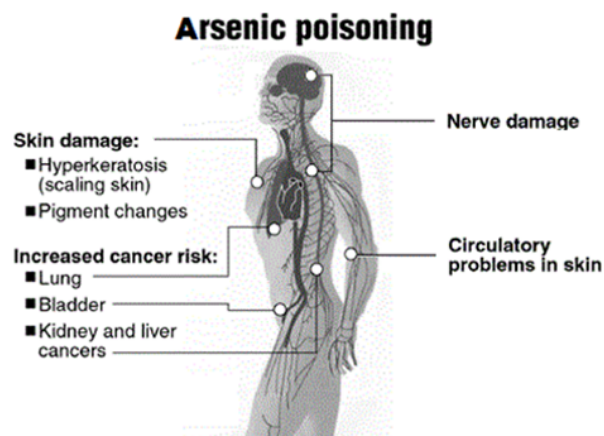


Fig. 2: Effect of arsenic on various body parts<sup>13</sup>

Overexposure to arsenic leads to a number of adverse physiological effects which include respiratory effects (laryngitis, tracheae bronchitis, rhinitis, pharyngitis, shortness of breath, chest sounds (crepitation and/or rhonchi), nasal congestion and perforation of the nasal septum,<sup>14</sup> Cardiovascular effects (Raynaud's disease, myocardial infarction, myocardial depolarization, cardiac arrhythmias, thickening of blood vessels and their occlusion and BFD, Haematological effects (Anaemia and leukopenia), gastrointestinal effects (Sub acute arsenic toxicity- mouth and throat, heartburn, nausea, abdominal pains and cramps, and moderate diarrhoea; Chronic toxicity- mild esophagitis, gastritis, or colitis with respective upper and lower abdominal discomfort Anorexia, mal-absorption),<sup>14</sup> Hepatic effects, Renal effects (Proximal tubule degeneration, haematuria and proteinuria,<sup>15</sup> oliguria, shock and dehydration with a real risk of renal failure,<sup>16</sup> cortical necrosis,<sup>17</sup> and cancer.<sup>18</sup>

### 1.5. Toxicity mechanism

Arsenic exerts its toxic effects by inactivation of various enzymes that are responsible for a number of cellular pathways and DNA replication and repair. Various mechanisms that relate to arsenic toxicity are oxidative

**Table 1:** Arsenic exposure and adverse health effects: A review of recent findings from arsenic and health studies in Matlab, Bangladesh (2011)<sup>18</sup>

Studies	Study Design	Characteristics Participants	Arsenic Measurements	Main Findings
Rahman et al.	Cross-sectional	All population aged 4 yr or older (166,934)	Water arsenic	Prevalence of skin lesion
Rahman et al.	Case-referent	All skin lesion cases (504) and randomly selected 1,830 individuals	Water arsenic	Skin lesion, dose-response trend, gender difference in risk
Jakariya et al.	Cross-sectional	Tube-well screening	Water arsenic	Public health importance
Hore et al.	Cross-sectional	All population aged 4 yr or older (166,934)	Water arsenic	Validity of detection skin lesion cases
Rahman et al.	Historical cohort	All pregnancy outcome during 1991-2000 (29,134)	Water arsenic	Fetal loss and infant deaths
Lindberg, Rahman et al.	Cross-sectional	Randomly selected 1,830 individuals	Urinary arsenic	Influence of factors on exposure and metabolism
Lindberg, Ekstrom et al.	Cross-sectional	Randomly selected 526 individuals	Urinary arsenic	Interaction between gender and arsenic metabolism
Sohel et al.	Historical cohort	All adult population aged 15 yr or older on 1 January, 1991 (115,903)	Water arsenic	Excessive mortality risk for cancer, cardiovascular, all infections and non-accidental deaths

stress, modification of cellular signalling, apoptosis, epigenetic modifications that results in abnormal gene expression, inhibition of DNA repair.<sup>19–21</sup> Arsenite increases the generation of ROS, which enhances lipid peroxidation and cellular damage in both hepatic and renal tissue.<sup>22</sup>

Most laboratory animals appear to be substantially less susceptible to arsenic than humans. It has been reported that chronic oral exposure to inorganic arsenic causes neurological and haematological toxicity in humans but not in monkeys, dogs, and rats exposed to arsenite or arsenate at doses of 0.72 to 2.8 mg/kg/day.<sup>23</sup>

Arsenic induced oxidative stress increases the expression of HO1 and MAPK, which by regulating various transcription factors such as activator protein1 (AP1), activating transcription factor2 (ATF2), and Elk1 lead to renal toxicity.<sup>24</sup> Acute renal dysfunction due to arsenic exposure is characterized by acute tubular necrosis and cast formation with increase in blood urea nitrogen and creatinine levels.<sup>25</sup>

The Millard County study reported an increased mortality from nephritis and prostate cancer. Guo et al. in 1997 analysed cancer registry data (1980–87) of tumours of the bladder and kidney in Taiwan and reported that high arsenic levels in drinking water from wells were associated with transitional cell carcinomas of the bladder, kidney, ureter and all urethral cancers in both males and females, and adenocarcinomas of the bladder in males. When As is administered alone it does not produce tumors in traditional animal models, but it can act as a carcinogen in animal models using fetal exposure paradigms because As crosses the placenta.<sup>26</sup>

As readily crosses the placenta, thus it may alter prenatal development. It is a well-known teratogen. In a human pregnancy case of arsenic trioxide poisoning it was documented that inorganic arsenic crosses human placenta with much ease and with extremely high levels in fetal liver, brain and kidney Lugo et al.<sup>27</sup> A comparative toxicity study of arsenic, copper and chromium concluded that arsenic (Sodium arsenate 5mg As/kg ip) was not found to be fetotoxic or either effect fetal weight or maternal toxicity but the incidences of fetal abnormalities were higher.<sup>28</sup>

### 1.6. Respiratory effects

Effects of arsenic on the human respiratory system have been reported both from occupational exposure as well as from tube well water arsenic toxicity. Humans exposed to arsenic dust or fume inhalation are more apt to be encountered in mining and milling of ores, in industrial processing, such as smelting industry which often produces irritation of the mucous membrane, resulting in laryngitis, bronchitis, rhinitis and tracheobronchitis, causing stuffy nose, sore throat, hoarseness and chronic cough etc.<sup>29</sup> Very high exposure to unprotected workers may manifest perforated nasal septum after 1-3 weeks of exposure,<sup>30</sup> but such effects are minor or absent at exposure levels of 0.01-1 mg/m<sup>3</sup>. A fatal case of arsenic trioxide inhalation manifested widespread tracheobronchial mucosal and sub mucosal haemorrhages with mucosal sloughing, alveolar haemorrhages, and pulmonary edema. Chronic asthmatic bronchitis and asthma is a common complication of ground water arsenic toxicity.<sup>31</sup>

### 1.7. Effects on kidney

Kidney is a target organ for heavy metals. They accumulate in several segments of the nephron and cause profound alterations in morphology and function. Due to its secretory mechanisms, tubular proximal cells are often exposed to higher concentrations of toxic substances than those occurring in plasma or extracellular fluids. Arsenic gets accumulated in the kidney during its urinary elimination that affects the function of proximal convoluted tubules. In addition to these functions, kidney also plays a critical role in the bio transformation of toxic compounds and neutralize their toxic effect and change the chemical properties so that they become soluble in the aqueous media and easily excreted from the body several mechanisms to absorb and excrete toxicants. Exposures in utero and early post-natal development may be important triggers for disease susceptibility and cause severe impairment of organ function in later life (Yeonjin lee et al.,2012).<sup>32</sup>

### 1.8. Cardiovascular effects

It has been suggested by several epidemiological studies that chronic inhalation of arsenic trioxide can increase the risk of death in humans from cardiovascular disease.<sup>33–35</sup> Long term inhalation of inorganic arsenic could injure the blood vessels or the heart. Zaldivar<sup>35</sup> reported several cases of myocardial infarction and arterial thickening in children who consumed water containing about 0.6 mg/l arsenic. Arsenic ingestion through food or water may have serious effects on the human cardiovascular system. Both acute and chronic arsenic exposure cause altered myocardial depolarization and cardiac arrhythmias that may lead to heart failure.<sup>36,37</sup> Low level arsenic exposure by humans may also cause vascular system damage, a classical example of which is Blackfoot disease, which is endemic in an area of Taiwan where most drinking water contains 0.17 to 0.8 ppm arsenic,<sup>38,39</sup> corresponding to doses of about 0.01 to 0.5 mg As/kg/day. In ground water arsenicosis of West Bengal this ischaemic gangrene from vasculitis are not seen probably due to less arsenic concentration circulating in blood stream.<sup>40</sup>

### 1.9. Renal effects

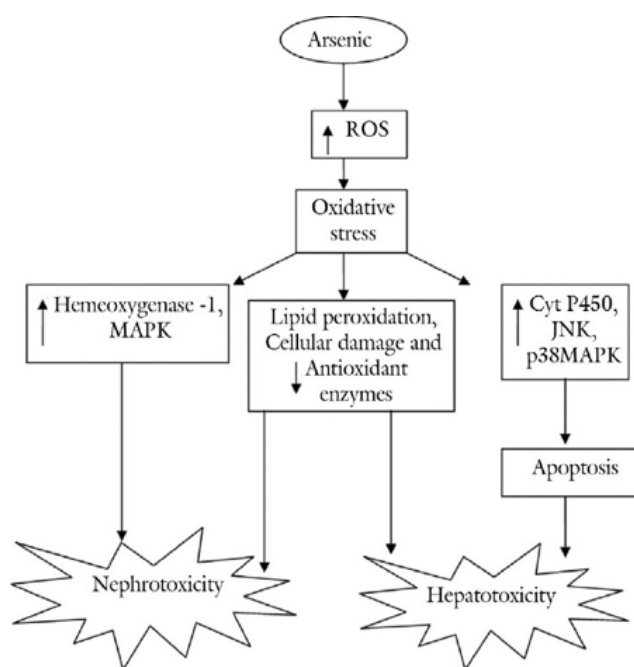
Like the liver, the kidneys will accumulate arsenic in the presence of repeated exposures. The kidneys are the major route of arsenic excretion, as well as major site of conversion of pentavalent arsenic into the more toxic and less soluble trivalent arsenic. Sites of arsenic damage in the kidney include capillaries, tubules, and glomeruli.<sup>41</sup>

### 1.10. Cellular mechanism

Arsenic induced toxicity is caused due to oxidative stress, altered cellular signaling cascade via altered expression

and interaction of transcription factors to its target molecules and DNA binding sites, altered epigenetic patterns thus resulting in abnormal gene expression. Possible mechanisms of arsenic induced carcinogenicity include genotoxic and cytotoxic mechanisms. Arsenic disrupts the genomic integrity of the cell via a complex network of aberrant signaling cascades and dysregulated transcription factors induced by arsenic mediated ROS generation. Arsenic also affects the native DNA methylation and Histone acetylation patterns.<sup>42</sup>

Many studies to demonstrate the mechanism of arsenic toxicity have suggested that reactive oxygen species and reactive nitrogen species are generated during inorganic arsenic metabolism in living cells. Arsenic shows a rapid decline of mitochondrial membrane potential and induces morphologic changes in mitochondrial integrity. Mitochondrial alterations are considered to be primary sites where an uncontrolled random formation of superoxide anion radical occurs. Experimental results based on both in vivo and in vitro studies of arsenic-exposed humans and animals suggest the possible involvement of increased formation of peroxy radicals (ROO), superoxide anion radical ( $O_2^-$ ), singlet oxygen ( $O_2^1$ ), hydroxyl radical (OH), hydrogen peroxide ( $H_2O_2$ ), dimethylarsenic radical [ $(CH_3)_2As$ ], blood nonprotein sulfhydryls and/or oxidant-induced DNA damage.<sup>42</sup>



**Fig. 3:** Cellular effects of arsenic<sup>43</sup>

In a study on HL-60 cells which were treated with varying concentration of arsenic trioxide (ATO) it was found that ATO-induced oxidative stress caused an increase in the expression level of pro-apoptotic proteins (Bax and

cytochrome C) and reduced the expression level of anti-apoptotic protein (Bcl-2), in a dose-dependent manner. Densitometric analysis has shown that ATO-induced apoptotic proteins, cytochrome C and Bax expression significantly ( $p < 0.05$ ) at 4 and 6  $\mu\text{g/ml}$  ATO treated HL-60 cells lysate (2B). Whereas, anti-apoptotic protein, Bcl-2 expression was significantly down regulated at 6 and 8  $\mu\text{g/ml}$  ATO treatment cells lysate (2B). Inside the cytosol, cytochrome C stimulates a series of apoptotic signaling molecules along with variety of caspases (like caspase 9) and finally caspase 3 which is main executioner of mitochondrial pathway of apoptosis.<sup>43</sup>

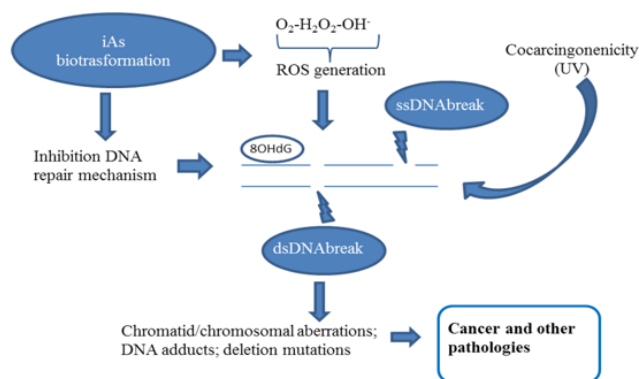


Fig. 4: Arsenic induced genotoxicity<sup>43</sup>

### 1.11. Toxicokinetics

#### 1.11.1. Absorption

90% absorption of ingested arsenic takes place through the gastrointestinal tract, wherein the major site of absorption is the small intestine. This absorption takes place through an electrogenic process involving a proton ( $\text{H}^+$ ) gradient.<sup>44</sup> The optimum pH required for the absorption of Arsenic is 5,<sup>45</sup> though the pH in the small intestine is approximately 7.0 due to the presence of pancreatic bicarbonate secretions.<sup>46</sup>

#### 1.12. Distribution

The bio availability of ingested inorganic arsenic varies depending on the matrix in which it is ingested (i.e. be it food, water, beverages or soil), the solubility of the arsenical compound itself and the presence of other food constituents and nutrients in the gastrointestinal tract. Tissue distributions of arsenic depend on blood perfusion, tissue volumes, diffusion coefficients, membrane characteristics, and tissue affinities.<sup>46</sup>

#### 1.13. Metabolism & elimination

The absorbed arsenic undergoes methylation reaction in the liver. The methylation process is mediated by arsenic

methyltransferase enzymes to form monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA).

DMA is the dominant metabolite according to many studies, while in human the urinary excretion consists under normal conditions, i.e. without excessive ingestion of inorganic arsenic—of about 20% inorganic arsenic, 20% MMA and 60% DMA.

## 2. Conclusion

Chronic exposure to arsenic from contaminated water may cause a variety of health problems. Arsenic promotes cardiovascular problems through increasing oxidative stress, up regulating pro inflammatory cytokines and inflammatory mediators, inactivating eNOS, and phosphorylating MLCK. The pathogenic events linked with arsenic-induced diabetes include decreased PPAR-expression, interference with ATP-dependent insulin secretion, altered glucocorticoid receptor-mediated transcription, and inhibition of PDK-1. Furthermore, oxidative stress, pyruvate decarboxylase inhibition, and acetyl cholinesterase appear to be important in arsenic-induced neurotoxicity. Furthermore, arsenic increases oxidative stress and apoptosis, causing nephrotoxicity and hepatotoxicity. Arsenic may also be carcinogenic because it causes oxidative DNA damage and chromosomal abnormalities, as well as interfering with cellular signalling networks. Targeting and modifying the aforementioned main pathogenic signalling systems could lead to new pharmaceutical approaches to treat arsenic-related diseases.

## 3. Source of Funding

None.

## 4. Conflict of Interest

None.

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