



# Cryptic exposure to arsenic

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### ABSTRACT

Arsenic is an odorless, colorless and tasteless element long linked with effects on the skin and viscera. Exposure to it may be cryptic. Although human intake can occur from four forms, elemental, inorganic (trivalent and pentavalent arsenic) and organic arsenic, the trivalent inorganic arsenicals constitute the major human hazard. Arsenic usually reaches the skin from occupational, therapeutic, or environmental exposure, although it still may be employed as a poison. Occupations involving new technologies are not exempt from arsenic exposure. Its acute and chronic effects are noteworthy. Treatment options exist for arsenic-induced pathology, but prevention of toxicity remains the main focus. Vitamin and mineral supplementation may play a role in the treatment of arsenic toxicity.

**Key Words:** Arsenic, Arsenicism, Carcinogenesis, Environmental toxins, Skin cancer, Bladder cancer, Lung cancer

### INTRODUCTION

Arsenic is a naturally occurring ubiquitous element.<sup>[1]-[5]</sup> It is an odorless, colorless, nearly tasteless element present in elemental, organic, and inorganic (trivalent and pentavalent) forms.<sup>[2],[5]-[7]</sup> The inorganic forms are more common sources of toxic exposure to arsenic, causing both acute and chronic effects on man, while the organic forms are generally thought to be much less toxic.<sup>[1],[6],[8],[9]</sup> The trivalent inorganic form of arsenic, arsenite [As (III)], and the pentavalent form, arsenate [As (V)], are both contaminants of groundwater and foods, but arsenite is the more toxic of the two.<sup>[7],[8],[10]</sup> The mechanism of toxicity is uncertain, but generation of free radicals or interference in the glutathione pathway causing oxidative stress has been hypothesized.<sup>[7]</sup> Trivalent arsenic, in the form of Fowler's solution ( $KAsO_2$ ), Asiatic pills ( $As_2O_3$ ), and Donovan's solution ( $AsI_3$ ), has also been used for medicinal purposes. Although pentavalent forms of

arsenic are not components of medical therapies, they are common in contaminated sources in nature. On ingestion, they are reduced to the trivalent form. Organic forms of arsenic are the predominant type identified in seafood.<sup>[1],[11],[12]</sup>

There are theories about the mechanisms in which arsenic is carcinogenic to humans, but there is limited proof to support them due to the lack of animal models. Animal research on the carcinogenicity of arsenic is not useful because arsenic does not induce cancer in these models.<sup>[10]</sup> In vivo cytogenetic assays of lymphocytes of humans exposed to arsenic show high levels of chromatid breaks, deletions and, to a lesser degree, chromosomal exchange. These correlations suggest that arsenic induces chromosomal aberrations in a dose-dependent manner.<sup>[10]</sup>

In nature, arsenic is frequently found in combination with other elements like sulfur, oxygen, and iron. The

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most common existing forms are orpiment ( $As_2S_3$ ), realgar (AsS), arsenopyrite (FeAsS), arsenolite ( $As_2O_3$ ) and lollingite ( $FeAs_2S_2$ ). These arsenic compounds commonly occur in gold, silver, copper, lead, zinc, cobalt, and tin ores.<sup>[8]</sup> Smelting of these compounds can release large quantities of arsenic into the environment, causing unrecognized contamination of the surrounding air, water, soil, and vegetation.<sup>[10]</sup>

For millions of people around the world, the source of chronic arsenic toxicity is usually cryptic, due to unknown environmental, occupational, or medicinal exposure.<sup>[7-18]</sup> Over the past 20 years there has been increased interest in arsenicism, resulting from increased awareness of toxic levels of arsenic in water and food supplies. India, Bangladesh, China, Argentina, Mexico, Pakistan, and Chile are the countries most affected by chronic exposure to arsenic via contaminated water supply.<sup>[9,10]</sup> After toxic levels of arsenic were identified in the 1980s, efforts have been made to clean the water supply in West Bengal, India and Bangladesh. Presently, concern is rising in neighboring areas such as the Gangetic Plains, Terai of Nepal, Padma-Meghna-Brahmaputra delta, Chandigarh region, and Bihar.<sup>[7,19]</sup> Efforts have been initiated to rectify this problem, but many of these countries lack the funds to support these efforts.<sup>[1]</sup>

## ENVIRONMENTAL AND MEDICINAL EXPOSURE

Groundwater contamination with arsenic is a worldwide concern. The World Health Organization has identified many regions with groundwater levels of arsenic that greatly exceed the limit of 50 micrograms per liter.<sup>[1],[6-12],[20],[21]</sup> As many as 42 million people in 9 out of 18 districts in West Bengal, India are exposed to high arsenic levels in their water supply.<sup>[22]</sup> For their groundwater supply, these people rely on tube wells. This water is used for drinking, cooking, and cleaning. These tube wells contain water contaminated with high levels of arsenic (there are some reports of arsenic levels as high as 3 milligrams per liter).<sup>[7],[21]</sup> It has been proposed that withdrawal of groundwater via tube wells results in oxidative and reductive reactions causing the decomposition of iron pyrites and release of arsenic.<sup>[11]-[12]</sup> In this region, rivers are being contaminated with arsenic as a result of redistribution

of groundwater during the monsoon.<sup>[19]</sup>

In West Bengal and Bangladesh, tube wells also supply the water used for irrigation.<sup>[1],[6-12],[21],[23]</sup> With the increase in population over the years in India and Bangladesh, irrigation-dependent agricultural systems have become necessary. As a result, high levels of arsenic have been reported in products that are considered staples, such as vegetables, rice, and herbs.<sup>[12],[21]-[23]</sup> Vegetables have high levels of arsenic absorbed in their skins, with lower levels found in the fleshy inner portions.<sup>[12],[21]</sup> Higher levels of arsenic are found in cooked items than in raw ones because of the use of contaminated water to rinse and cook vegetables.<sup>[21]</sup>

Arsenic present in food composites is a matter of concern for both humans and animals. Arsenic-contaminated groundwater is often used in Bangladesh and West Bengal to irrigate crops used for food and animal consumption and high concentrations of arsenic have been reported in the rice crops in these areas. Both humans and cattle feed on rice crops, and high levels of arsenic are found in both groups.<sup>[24]</sup> Arsenic could enter the human food chain wherever this food is consumed, including countries as distant as the United Kingdom.<sup>[23]</sup> In Canada, USA, and Japan, the highest levels of organic arsenic are in seafood.<sup>[6],[12],[21]</sup> High concentrations of arsenic have also been noted in “moonshine”, an illegally produced potent alcoholic beverage.<sup>[25]</sup>

Medicinal exposure to arsenic has been significant since the past few centuries [Table 1]. Arsenic was first introduced into the US Pharmacopoeia in 1850, with the use of arsenous iodide and a solution of arsenous and mercuric iodide.<sup>[25]</sup> In Europe and the USA, arsenic compounds, such as Fowler’s solution and Asiatic pills, were used as medications until 1965 to treat leukemia, psoriasis, asthma, pemphigus, pernicious anemia, and Hodgkin’s disease.<sup>[26],[27]</sup> Today, arsenic use continues with medications such as arsenic trioxide (Trisenox), used for the treatment of acute myeloid leukemia.<sup>[8],[27],[28]</sup> Cases have been reported from China and Singapore of chronic arsenic poisoning from anti-asthmatic herbal preparations that contain inorganic arsenic sulfide, and from other medicinal tonics.<sup>[29]</sup>



**Table 1: Source of cryptic arsenic exposure**

Environmental/Medicinal	
•	Contaminated well water
•	Fowler's solution (1% $KAsO_2$ )
•	Asiatic pills
•	Health tonics
•	Donovan's solution ( $AsI_3 + HgI_2$ )
Occupational	
•	Mining and smelting
•	Wine-making
•	Carpentry
•	Agriculture
•	Computer chip production
•	Electroplating
•	Marine plywood
•	Fishermen eating contaminated seafood

Arsenic has been used with opium in India as an aphrodisiac and in herbal remedies for various illnesses.<sup>[30],[31]</sup> Asian immigrants have been reported to import powdered blends of folk remedies that are high in arsenic sulfide.<sup>[32]</sup> Chronic arsenic toxicity can also result from intentional poisoning over an extended period of time.

Another subtle cause of arsenic poisoning is the burning of chromium copper arsenate (CCA) treated wood.<sup>[9],[33]</sup> There have been suggestions of a link between the use of CCA-treated wood to build decks and playgrounds and possible arsenic toxicity. There is concern about children's exposure to the arsenic that leaches from these structures.<sup>[34]</sup> A recent soil analysis study indicated that arsenic does not migrate laterally but accumulates under elevated platforms at levels that can exceed the soil guideline. Chronic arsenic exposure may increase the risk of fetal and infant death.<sup>[35]</sup> CCA-treated wood is banned in Europe, Asia, and the USA.<sup>[36],[37]</sup> There is increased research to determine the appropriate method to dispose wood high in arsenic and chromium in landfills, and to identify safe and effective alternatives for playgrounds and decks.<sup>[36],[37]</sup>

In Taiwan, a significant dose-response trend in lung cancer risk was identified in those who had ingested arsenic, and this was more prominent in cigarette smokers.<sup>[38]</sup>

### OCCUPATIONAL EXPOSURE

In 1973 it was reported that over 1.5 million workers

in America alone in various occupations were being exposed to inorganic forms of arsenic, either directly or via contaminated water or soil.<sup>[16]</sup> Mining is one activity with an increased risk of arsenic exposure, since arsenic is an element that coexists with gold, cobalt, zinc, lead, and coal. There is also an increased risk of arsenic toxicity with smelting of non-ferrous metal ores, which produces an arsenic byproduct.<sup>[4]</sup> Smelter workers in Sweden have been found to have higher levels of arsenic in their bodies when compared to control subjects.<sup>[10]</sup> Abrasive blasting operations, both indoors and outdoors, with copper slag abrasive contribute to arsenic exposure and possible toxicity.<sup>[39]</sup>

In America arsenic has played a big role in agricultural practice, and has been used in pesticides, herbicides, insecticides, rodenticides, desiccants, and feed additives.<sup>[40]</sup> Worldwide, arsenic continues to be used in pesticides and fungicides to treat small gardens. Cases of chronic arsenicism have been reported in Germany in areas where such pesticides were used on vineyards.<sup>[2],[41]</sup>

With advances in technology, new opportunities for arsenic use and exposure have arisen. For example, computer microchips have improved in speed by using gallium arsenide in place of silicon substrates.<sup>[42]</sup> Arsenic and other toxic elements are commonly used in the optoelectric industry, and high levels of arsenic, exceeding the safety range, have been measured in workers' blood and urine.<sup>[43]</sup> Arsine and gallium arsenide are both commonly used in the microelectronics industry. Highly insoluble arsenide semiconductors are less toxic acutely when compared to arsine and other more soluble forms, but gallium arsenide causes more lung damage than other compounds.<sup>[44]</sup> Advances in technology have been accompanied by an increased risk of arsenic exposure for workers. The risk of arsenic toxicity can be effectively minimized by worker education and implementation of safety precautions.<sup>[43]</sup>

Another unusual cryptic occupational exposure may occur in an emergency room setting.<sup>[45]</sup> In a suicide attempt a patient may ingest arsenic trioxide. Gastric lavage may then be employed, but most of the poison may remain in the stomach. A total gastrectomy may then be performed, exposing medical staff members



to fumes from the patient's stomach. This may lead to the development of corneal erosion or laryngitis because arsenic trioxide reacts with stomach acid to produce arsine.<sup>[45]</sup> Protective measures to safeguard medical staff from exposure to arsine gas during the treatment of patients poisoned from ingested arsenic trioxide are desirable.

## CLINICAL MANIFESTATIONS

Arsenicism is a systemic disease that mainly affects the skin, nervous system, gastrointestinal system, and blood.<sup>[2],[9],[17],[18],[29]</sup> Acute arsenic toxicity can cause gastrointestinal discomfort, with nausea, vomiting, and diarrhea. Death is a potential result. *Edema arsenicalis* can be present, with swelling of the face and eyelids. An asymmetric peripheral neuropathy can occur, resembling the Guillain-Barré syndrome.<sup>[9],[46]</sup> Mees' lines, white transverse bands that usually affect all fingernails, can be identified after 2 months of arsenic exposure, allowing for identification of exposure.<sup>[9],[17],[47]</sup> Brown discoloration of the nails can also occur.<sup>[47]</sup>

Common dermatological manifestations of chronic arsenic toxicity are diffuse or spotted melanosis, palmar and plantar keratoses, and leukomelanosis.<sup>[9],[17],[47],[48]</sup> Chronic exposure to arsenic can cause alteration of skin pigmentation and keratoses that can potentially progress to Bowen's disease or squamous cell or basal cell carcinomas.<sup>[10],[17],[18],[20],[48]</sup> Hematological disruption may result, with possible anemia, leukopenia, and thrombocytopenia. Peripheral vascular disease (black foot disease), cardiovascular disease, diabetes, and reproductive difficulties can all result from chronic arsenic exposure.<sup>[1],[9],[48]</sup> Cases of non-cirrhotic portal hypertension, hepatocellular carcinoma and angiosarcoma of the liver have been reported.<sup>[9],[48]</sup>

Lung, bladder, and kidney malignancies have also been reported in chronic arsenicism.<sup>[48]</sup> A study in Finland showed a link between chronic low exposure levels of arsenic and the occurrence of bladder cancer.<sup>[49]</sup> Evidence from this study also suggested a synergistic effect of arsenic and cigarette use on the development of bladder cancer.<sup>[49]</sup> A study in Taiwan found a dose-response relationship between chronic arsenic exposure through well water and an increased

incidence of lung and bladder cancer.<sup>[50]</sup> Another study that confirmed a relationship between arsenic ingestion and occurrence of liver, bladder, and lung cancer, also noted a higher incidence of lung cancer among copper smelter workers.<sup>[51]</sup> Myelogenous leukemia may also occur due to chronic toxic exposure to arsenic, "although paradoxically" at lower levels arsenic trioxide is used to treat acute myeloid leukemia.<sup>[9],[27]</sup>

## TREATMENT

Chelating agents, such as dimercaprol, dimercaptosuccinic acid, and dimercaptopanesulfonic acid, can remove arsenic but are only effective while traces of arsenic remain in the body.<sup>[9],[52]</sup> Chronic cutaneous arsenicism and arsenic-induced basal cell carcinomas can be treated with oral retinoid therapy.<sup>[53]</sup> The main localized treatment options that are effective for arsenical keratoses are excisional surgery, cryosurgery, electrodesiccation and curettage, and topical chemotherapy.<sup>[17],[54],[55]</sup>

## PREVENTION

Prevention of arsenic toxicity through reducing environmental and occupational exposure is key. Efforts need to be continued to ensure that levels of arsenic in water sources are tested and maintained within the acceptable range. Safety precautions when working in occupations with potential exposure should be enforced. CCA-treated wood should not be burned and should not be used. Good nutrition may also play a role in preventing and treating arsenic toxicity.<sup>[1],[7],[9],[11],[12],[21]</sup> Levels of selenium and zinc are low in those suffering from the effects of chronic arsenic exposure, suggesting a role for selenium and zinc supplementation.<sup>[7],[11],[12]</sup> Correlations have been made between increased levels of vitamin C and methionine and lower arsenic toxicity, increased sensitivity to arsenic with vitamin A deficiency, and increased toxic effects with diets high in carbohydrates or fats.<sup>[21]</sup>

Chronic arsenicism represents an important cutaneous sign of internal cancer. Since exposure to arsenic is often cryptic, clinical traces of arsenic are often long gone and the carcinogenic lag may be up to 50 years, it is important to have an elevated index of suspicion

for diagnosis of arsenicism in appropriate clinical and environmental settings.

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## ANNOUNCEMENT

**Pemphigus and Pulse Therapy Foundation**  
is Organizing a Symposium on  
**Pulse therapy (D.C.P./ D.P.) in Dermatology**

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