Inorganic Arsenic

Toxicological overview

Key Points

**Kinetics and metabolism**

- Absorption of arsenic is largely dependent on the solubility and particle size
- Concentrations of arsenic or its metabolites in blood, hair, nails and urine may be used as biomarkers of arsenic exposure
- Blood arsenic is a useful biomarker only in the case of acute arsenic poisoning or stable chronic high-level exposure
- Since the elimination of arsenic takes place mainly via the kidneys, the concentration of arsenic in the urine is a good indication of recent exposure to inorganic arsenic

**Health effects of acute exposure**

- Single doses of inorganic arsenic may be highly toxic by ingestion and inhalation
- Both ingestion and inhalation may cause gastrointestinal effects such as nausea, diarrhoea and abdominal pain
- Multi-organ failure may occur in severe cases following ingestion
- Inorganic arsenic is irritant to the eye and skin

**Health effects of chronic exposure**

- Following chronic ingestion a range of non-specific symptoms of the respiratory tract, CNS, endocrine system, liver, kidneys or gastrointestinal system may occur
- Chronic inhalation of arsenic may cause irritation of the mucous membranes leading to conjunctivitis, pharyngitis and rhinitis
- Inorganic arsenic compounds have mutagenic potential
- Inorganic arsenic is a known human carcinogen which acts via a genotoxic mechanism
Toxicological Overview

Summary of Health Effects

Single doses of inorganic arsenic may be highly toxic by ingestion and inhalation (70-180 mg orally has been fatal). Trivalent arsenic is, in general, more toxic than pentavalent arsenic [1].

Inorganic arsenic is a known human carcinogen which acts via a genotoxic mechanism [2]. It is assumed, therefore, that there is no threshold for such effects and that risk management measures should ensure that exposures are as low as reasonably practical. There is sufficient evidence that chronic exposure to inorganic arsenic in drinking water causes non-melanoma skin cancers and an increased risk of bladder and lung cancers in humans.

The effects of inorganic arsenic on the vascular periphery are well documented. Long-term ingestion of contaminated drinking water may lead to, Raynaud's phenomenon and acrocyanosis and progression to endarteritis obliterans and gangrene of the lower extremities (“Black foot disease”). An increased incidence of cardiovascular disease has also been noted. Haematologically, anaemia and leucopenia may occur together with disturbances in haem synthesis.

Chronic exposure to inorganic arsenic compounds may lead to peripheral and central neurotoxicity [1]. Early events may include paresthesiae followed by muscle weakness. In the periphery, both motor and sensory neurones are affected.

Characteristic dermal lesions after chronic oral or inhalation exposure may include hyperpigmentation and hyperkeratosis.

Other toxic effects associated with chronic exposure to inorganic arsenic include liver injury, cardiovascular disease and diabetes mellitus.

There is limited data from epidemiology to suggest that inorganic arsenic may be a human developmental toxicant, but it is not possible to draw any definitive conclusions. Administration of high doses of inorganic arsenic by oral, intraperitoneal or intravenous routes may cause embryolethality or foetal malformations in laboratory animals.

Inorganic arsenic may cause irritation of the mucous membranes leading to conjunctivitis and pharyngitis and rhinitis after inhalation. Skin irritation and allergic contact dermatitis may occur after exposure to inorganic arsenic compounds.
**Kinetics and metabolism**

Absorption of arsenic in inhaled airborne particles is highly dependent on the solubility and the size of particles; material that reaches the lungs will be well absorbed. Studies in experimental animals and humans have shown that both soluble pentavalent and trivalent arsenic compounds are rapidly and extensively absorbed from the gastrointestinal tract (over 90%); these include arsenious acid and sodium arsenite [1, 3]. Insoluble compounds such as arsenic disulphide are poorly absorbed.

Inorganic arsenic compounds react with sulphhydryl (SH) groups of cellular proteins, thereby inhibiting enzymes and therefore oxidative processes including pyruvate and succinate pathways [4].

Arsenic metabolism is characterized by two main types of reactions: (a) reduction reactions of pentavalent to trivalent arsenic, and (b) oxidative methylation reactions in which trivalent forms of arsenic are sequentially methylated to form mono-, di- and trimethylated products using S-adenosyl methionine (SAM) as the methyl donor and glutathione (GSH) as an essential co-factor [5].

Methylated products (MMA and DMA) are readily excreted in urine. Animal and human studies suggest that arsenic methylation may be inhibited at high acute exposures.

The metabolism and disposition of inorganic arsenic may be influenced by its valence state, particularly at high dose levels. Studies in laboratory animals indicate that administration of trivalent arsenic, such as arsenic trioxide, results initially in higher concentrations in most tissues than does the administration of pentavalent arsenic. However, the trivalent form is more extensively methylated, leading to similar long-term excretion.

Concentrations of arsenic or its metabolites in blood, hair, nails and urine may be used as biomarkers of arsenic exposure. Blood arsenic is a useful biomarker only in the case of acute arsenic poisoning or stable chronic high-level exposure [1]. Since the elimination of arsenic takes place mainly via the kidneys, the concentration of arsenic in the urine is a good indication of recent exposure to inorganic arsenic [3].

**Sources and route of human exposure**

Dietary arsenic is the key source of intake for most of the population. Arsenic in the diet is predominantly organic, which is much less toxic than inorganic arsenic. Total arsenic (organic and inorganic species) in fish and shellfish may be higher than most foods; however, inorganic arsenic constitutes less than 1% of this total [6].

High levels of arsenic may be found in water from wells, notably in Bangladesh, West Bengal in India, Taiwan and Hungary.

Workers at smelting plants or residents nearby may be exposed to higher than normal levels of arsenic. Individuals sanding or burning wood preserved with inorganic arsenic may come into contact with vapours or dusts containing inorganic arsenic.

Systemic toxicity may occur after inhalation, ingestion or topical exposure to inorganic arsenic.
Health Effects of Acute / Single Exposure

**Human Data**

**Inhalation**

Due to the irritant nature of a number of inorganic arsenic compounds, rhinitis, pharyngitis, laryngitis, and tracheobronchitis may occur. Tracheal and bronchial haemorrhage may complicate severe cases [4]. Gastrointestinal effects including nausea, diarrhoea and abdominal pain have been associated with inhalation of arsenical dusts.

**Ingestion**

Ingestion of large doses of arsenic may lead to acute symptoms within 30-60 min; effects may be delayed when the arsenic is taken with food. An acute gastrointestinal syndrome is the most common presentation of acute arsenic poisoning characterised by a metallic or garlic-like taste associated with dry mouth, burning lips and dysphagia [1, 7]. Violent vomiting may ensue and may eventually lead to haematemesis. CNS findings may include headaches, weakness and delirium. Gastrointestinal symptoms caused by paralysis of the capillary control in the intestinal tract may include profuse watery diarrhoea and may lead to a decrease in blood volume, lowered blood pressure and electrolyte imbalance. Thus, after the initial gastrointestinal problems, rhabdomyolysis and multi-organ failure may occur, including renal failure, respiratory failure, failure of vital cardiovascular and brain functions, and death [1].

In humans, the smallest recorded fatal oral dose is approximately 70-180 mg [3]. Inorganic arsenic crosses the placental barrier and foetal death has been reported following acute maternal intoxication [4]. A 22 year old, at 20 weeks gestation, attempted suicide by ingesting 340 mg of sodium arsenate. After intensive therapy, the fetus survived and was delivered at 36 weeks [8].

**Dermal / ocular exposure**

Arsenic trioxide is irritant to the skin and mucous membranes. Pain, lacrimation, blepharospasm, conjunctivitis and corneal damage may occur after exposure to dusts or vapours containing inorganic arsenic. Corrosive compounds such as arsenic trichloride may pose a risk for systemic toxicity due to enhanced absorption through damaged skin.

**Delayed effects following an acute exposure**

Survivors of acute toxicity often develop bone marrow suppression (anaemia and leucopenia), haemolysis, hepatomegaly, melanosis and polyneuropathy resulting from damage to the peripheral nervous system.

Central and peripheral polyneuropathy is usually more severe in the sensory nerves, but may also affect the motor neurones [9, 10]. In common with other heavy metals, cognitive impairment and behavioural changes may occur. Skin lesions typical of chronic arsenic poisoning may also occur; hyperkeratosis and “rain-drop” pigmentation. Single or multiple
transverse white lines on the nails (“Mee’s lines”) may appear several weeks after absorption [4].

**Animal and In-Vitro Data**

**General toxicity**

The toxic action of inorganic arsenic in experimental animals resembles that seen in man.

**Inhalation**

In one study, rats were dosed with gallium arsenide and arsenic trioxide (100 and 17 mg kg\(^{-1}\), respectively) via the trachea to simulate inhalation. Findings included a significantly increased wet and dry lung weight, increased wet lung weight/body weight ratio and an elevation in total pulmonary protein, 4-hydroxyproline content and DNA; all suggestive of an acutely fibrogenic effect in the lung. Histopathological analysis of the lungs showed that there was an inflammatory response and pneumocyte hyperplasia, which resulted in thickening of the alveolar walls [1].

**Ingestion**

The oral LD\(_{50}\) of arsenic ranges from 15 to 293 mg kg\(^{-1}\) in rats, and from 11 to 150 mg kg\(^{-1}\) in other experimental animals [3]. Symptoms observed from arsenic trioxide intoxication in the rat include convulsions, retching and haemorrhaging in the intestinal tract [1].

**Dermal / ocular exposure**

Inorganic arsenic compounds may be highly irritating to both skin and eye, and lethality has been noted after administration using standard regulatory tests. Studies in guinea pigs did not yield evidence of a sensitization reaction to inorganic arsenic [10].
Health Effects of Chronic / Repeated Exposure

Human Data

It is pertinent to note that many of the chronic toxicities reported in humans are derived from studies that consider areas of the world where arsenic occurs at high concentrations in well water (tens, hundreds or even thousands of micrograms per litre) [2].

In the UK, arsenic in drinking water is not to exceed 10 µg L⁻¹ [11], and so this finding is unlikely to present clinically, but may be seen in immigrants from affected areas such as parts of Taiwan, South America, West Bengal in India or Bangladesh.

General toxicity

Signs of chronic toxicity may be difficult to diagnose: a number of body systems may be affected and to different extents. The onset after chronic exposure is insidious with a range of non-specific symptoms reported such as abdominal pain, diarrhoea, vomiting, weight loss and sore throat.

Table 1: Summary of key effects observed in humans after chronic arsenic exposure.

<table>
<thead>
<tr>
<th>System or Organ</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Tract</td>
<td>Inflammation and tracheobronchitis</td>
</tr>
<tr>
<td>Dermal</td>
<td>Hyperkeratosis and changes to pigmentation (melanosis)</td>
</tr>
<tr>
<td>Vascular</td>
<td>Peripheral vascular disease; (“Blackfoot disease”), myocardial injury</td>
</tr>
<tr>
<td>Haematological</td>
<td>Bone marrow depression (resulting in leucopenia and anaemia)</td>
</tr>
<tr>
<td>Neurological</td>
<td>Peripheral neuropathy, encephalopathy</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatomegaly, cirrhosis, altered haem metabolism</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Proximal tubule degeneration, papillary and cortical nephrosis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhoea, vomiting</td>
</tr>
</tbody>
</table>

Inhalation

Inorganic arsenic may cause irritation of the mucous membranes leading to conjunctivitis, pharyngitis and rhinitis and perforation of the septum [5]. Another syndrome noted in smelter workers includes symptoms of tracheobronchitis and signs of pulmonary insufficiency, often due to emphysematous lesions. This picture was found especially among those who had received mixed exposure to arsenic and sulphur dioxide [12].

Dermal changes are major indicators of chronic arsenic toxicity following inhalation or oral exposure (see below).

Although there is good evidence that acute arsenic poisoning causes neurological effects, especially in the peripheral nervous system, there is little evidence of neurological effects
from long-term lower-level environmental or occupational exposure. The few published studies have suggested changes in peripheral nerve function after arsenic exposure, but the studies have been limited by small numbers, different methods used to assess the endpoints and co-exposure to other known neurotoxins [1].

**Ingestion**

Symmetrical hyperkeratoses of the palms and soles, as well as melanosis and exfoliative dermatitis are major indicators of chronic arsenic toxicity following oral or inhalation exposure, but may take years to develop. The skin changes may progress and cover the entire body in multiple forms, and eventually develop into skin cancer [10]. The LOAEL (lowest observed adverse effect level) that results in dermal lesions following oral exposure has been estimated at between 10-100 µg kg day\(^{-1}\) [13].

Perivascular effects of inorganic arsenic in humans are well documented [1]. Long-term ingestion of contaminated drinking water may lead to acrocyanosis, Raynaud’s phenomenon (a peripheral vascular disease characterized by spasm of the digital arteries and numbness of the fingers). In extreme cases, this may progress to endarteritis obliterans and gangrene of the lower extremities (“Black foot disease”). Anaemia and leucopenia may occur together with disturbances in haem synthesis. An increased incidence of myocardial injury, cardiac arrhythmias and cardiomyopathy and cerebrovascular disease (especially cerebral infarction) has been associated with exposure to inorganic arsenic [1].

There is evidence that chronic arsenic ingestion may cause neurological effects, especially in the peripheral nervous system [2]. Signs and symptoms may include motor paralysis, tingling of the skin of extremities, foot and wrist drop, tremors, severe pain and ataxia [3]. In common with other heavy metals, cognitive impairment and behavioural changes may occur. A NOAEL (No observed adverse effect level) of 0.7 µg kg day\(^{-1}\) inorganic arsenic in drinking water has been derived using neurological effects as the reported adverse effect [13].

There is suggestive evidence of an increase in the incidence of diabetes mellitus [1] in response to chronic arsenic exposure and hepatic and renal injury. Non-specific gastrointestinal effects including diarrhoea and vomiting have been seen in chronic arsenic poisoning.

**Dermal / ocular exposure**

Allergic contact dermatitis may occur from repeated dermal exposure and is frequently seen among workers who are exposed to arsenic trioxide [3]. A study of 11 workers at a tin smelting factory where arsenic trioxide levels ranged from 5.2 to 14.4 mg m\(^{-3}\) showed generalized itch, dry and hyper-pigmented skin, folliculitis, and superficial ulcerations [10]. Conjunctivitis may also occur after exposure to vapours or dusts containing inorganic arsenic [10].

**Genotoxicity**

Inorganic arsenic compounds clearly have mutagenic potential [13]. In humans, arsenic is a chromosomal mutagen (an agent that induces mutations involving more than one gene, typically large deletions or rearrangements). Arsenic appears to have limited ability to induce point mutations. However, elevated frequencies of micronuclei, chromosomal aberrations
and aneuploidy have been detected in the peripheral lymphocytes or urothelial cells, or both, of people exposed to elevated levels of arsenic [2].

**Carcinogenicity**

IARC have classified inorganic arsenic as a known human carcinogen [2].

Chronic inhalation of inorganic arsenic can cause cancer in humans. A number of studies have shown good correlations between occupational exposure to arsenic and cancer in workers in such environments as copper smelting plants [1]. In one study, an almost ten-fold increase in the incidence of lung cancer was found in workers most heavily exposed to arsenic [14]. Smelter workers are however, exposed to other factors in the working environment, some of which may be carcinogenic. An attempt was made to control for exposure to sulphur dioxide, copper, lead, nickel, selenium, antimony and bismuth in one case-control study, and the excess lung cancer remained. Smoking habits have also been considered in two studies and could not account for the excess of lung cancer noted [15]. With regard to histological type of lung cancer, a significant, relative excess of adenocarcinomas and a slight excess of oat-cell cancers were seen among smelter workers [14].

Long-term ingestion of drinking water contaminated with inorganic arsenic has been causally linked to an increased risk of a number of other cancers [1]. However, in the most recent IARC review in 2004 there was considered to be sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin only [2].

The skin cancers induced by arsenic are of the non-melanoma type such as Bowen's disease, a squamous cell epithelioma *in situ* [2].

**Reproductive and developmental toxicity**

The effects of chronic inorganic arsenic on human reproduction are unclear. An association between inhalation exposure to arsenic and an increased risk of adverse developmental effects (foetal, neonatal and postnatal mortality, spontaneous abortions, lowered birth weight, congenital malformations and stillbirths) as well as pre-eclampsia has been reported in several epidemiological studies. In all of these there was also exposure to other chemicals and risk factors, which could have contributed towards the observed effects and there is no consistent evidence for any one particular end-point [1, 13].

**Animal and In-Vitro Data**

**General toxicity**

Long-term administration has produced liver lesions, anaemia, and pathological skin changes in animal models [3].

**Genotoxicity**

*In-vitro* studies to investigate the ability to induce point mutations are largely negative [1]. However, positive results were obtained in a number of studies to investigate clastogenicity
In in-vitro studies, inorganic arsenic compounds clearly have mutagenic potential [13].

Inorganic arsenic induces sister chromatid exchanges, chromosomal aberrations and DNA-protein cross-links in human lymphocytes and fibroblasts. These effects are dose-dependent, and sodium arsenite is more potent than sodium arsenate [1].

Clastogenic activity has also been consistently demonstrated in-vivo when inorganic arsenic compounds have been investigated in the bone marrow of mice [1].

**Carcinogenicity**

There is limited evidence for the carcinogenicity of sodium arsenite, calcium arsenate and arsenic trioxide and inadequate evidence for the carcinogenicity of sodium arsenate and arsenic trisulphide [2]. There is limited evidence that supports the carcinogenicity of inorganic arsenic from ingestion, which may in part be due its metabolism [14].

Arsenic trioxide has induced low incidences of carcinomas, adenomas, papillomas and adenomatoid lesions of the respiratory tract in hamsters after intratracheal instillation. A high incidence of lung carcinomas was induced in rats following a single intratracheal instillation of a pesticide mixture containing calcium arsenate. Intratracheal instillations of calcium arsenate into hamsters resulted in a borderline increase in the incidence of lung adenomas, while no such effect was observed with arsenic trisulphide. Sodium arsenite enhanced the incidence of renal tumours induced in rats by intraperitoneal injection of N-nitrosodiethylamine [14].

**Reproductive and developmental toxicity**

Administration of high doses of inorganic arsenic by oral, intraperitoneal or intravenous routes may cause embryolethality, increased resorptions or foetal malformations in laboratory animals [1].

The major teratogenic effects induced by inorganic arsenic in laboratory animals are neural tube defects. The malformations seen are dependent on the dose of arsenic administered as well as the gestational age. Sodium arsenite is a more potent teratogen than sodium arsenate, and parenteral administration of inorganic arsenic is more effective than oral administration. Administration of an acute oral dose of arsenite that is toxic to or near the lethal dose of pregnant mice (40–45 mg kg⁻¹) or hamsters (20–25 mg kg⁻¹) induces a low incidence of teratogenic malformations [1].

An oral study in mice found no significant impact on reproductive success. However, a slightly altered male: female ratio and a slight trend towards a smaller number of pups per litter were noted [13].
References


This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.