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Arsine and Stibine

Toxicological Overview

Key Points

Kinetics and metabolism

- arsine and stibine are readily absorbed following inhalation
- following absorption arsine and stibine are distributed to organs including blood, liver, kidneys and spleen
- arsine is oxidised to trivalent arsenic as well as pentavalent arsenic
- arsine metabolites are predominantly excreted in the urine

Health effects of acute exposure

- the characteristic toxic effect of both arsine and stibine is haemolysis
- the onset of symptoms may be delayed for several hours
- inhalation of arsine or stibine may cause headache, malaise, weakness, dizziness, dyspnoea, anaemia, red staining of the conjunctiva, dark red urine, abdominal pain, nausea and vomiting; renal failure, liver damage and pulmonary oedema may occur 24–48 hours post-exposure

Health effects of chronic exposure

- the effect of chronic exposure to arsine is expected to be similar to that of acute exposure
- there is no substantial evidence to suggest that arsine is a reproductive or developmental toxicant
- there is no data on the carcinogenicity of arsine itself, but it is metabolised to inorganic compounds that are recognised human carcinogens
- the carcinogenicity and reproductive effects of stibine have not been studied

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Summary of Health Effects

Arsine

Following acute inhalation of arsine the onset of effects may be delayed for several hours. Effects include headache, malaise, weakness, dizziness, dyspnoea, red staining of the conjunctiva, abdominal pain, nausea and vomiting. A characteristic effect is damage to red blood cells resulting in the release of haemoglobin. Dark red urine (due to the presence of haemoglobin) generally develops within 4–6 hours post-exposure. Anaemia, renal failure, liver damage and pulmonary oedema may develop 24–48 hours post-exposure. Exposure to high concentrations can lead to death. Peripheral neuropathy may develop over the first months following acute exposure to arsine. The effects of chronic exposure to arsine are similar to those observed following acute exposure.

The International Agency for Research on Cancer (IARC) has classified arsenic and arsenic compounds as known human carcinogens (Group 1). However, there is no data available on the carcinogenicity of arsine per se.

Stibine

The toxic effects of acute exposure to stibine are thought to resemble those associated with arsine exposure. Effects include headache, nausea, weakness, abdominal and lumbar pain, haematuria and haemolytic anaemia. There is currently no data available on the effects of chronic exposure to stibine in humans.

Kinetics and Metabolism

Arsine

Arsine is readily absorbed by the lungs and mucous surface of the respiratory tract following inhalation [1]. It is lipid soluble, therefore it diffuses rapidly across the alveolar and capillary membranes of the lungs and the red blood cell membrane [2]. Following exposure to arsine, the concentration in the blood increases rapidly, where it is preferentially bound to the red blood cell membrane. Distribution to the liver, kidneys, spleen and other organs is much slower [1].

Following absorption, arsine is oxidised to trivalent arsenic as well as pentavalent arsenic. Trivalent arsenic is subsequently methylated to monomethylarsonate and dimethylarsinate [1].

Arsine metabolites are predominantly excreted in the urine [1, 2]. The highest urinary excretion occurred within the first 5 days following an acute occupational exposure to arsine [1].

Stibine

Stibine is readily absorbed following inhalation. Following exposure, stibine has been detected in blood, liver, lungs, kidneys, thyroid, adrenals and pancreas [3].

Sources and Route of Human Exposure

Arsine

Inhalation of arsine is the major route of exposure. Arsine is formed whenever nascent hydrogen is generated in the presence of arsenic or when water reacts with metallic arsenides [4].

Many industrial processes including the smelting and refining of metals, plating, galvanising and soldering can lead to the accidental formation and liberation of arsine fumes [2]. Very small amounts of an arsenic impurity can lead to the formation of highly toxic levels of arsine. Occupational exposure may also occur in the lead acid battery industry or the semiconductor industry where arsine is extensively used as a doping agent. Arsine can be generated from other arsenic compounds (arsenites and arsenates) by some fungi and bacteria [1, 4]. Arsine formation is also thought to occur in the environment in places such as hazardous waste deposits [1].

Following exposure to light or when it comes into contact with moisture in the air arsine decomposes quickly, depositing shiny black arsenic. When exposed to water it rapidly hydrolyses to other arsenic compounds [1].

Stibine

Inhalation of stibine is the major route of exposure. Stibine is formed when alloys containing antimony are treated with acid and subjected to electrolytic action, when antimony compounds are treated with steam or whenever nascent hydrogen comes into contact with metallic antimony or a soluble antimony compound [3, 5]. Stibine is also generated during lead battery manufacture or results from overcharging of lead storage batteries. Exposure may also occur in the semiconductor industry where stibine is used as a doping agent [3].

Health Effects of Acute/Single Exposure

Human data

General toxicity

Arsine

Arsine primarily targets the erythrocyte (red blood cell) and rapidly induces intravascular haemolysis. Secondary effects resulting from haemolysis include haemolytic anaemia, hepatic and renal damage. The exact mechanism by which arsenic causes erythrocytes to rupture is not known, but it is believed to be due to either oxidative damage or reaction with sulphydryl groups [1].

Stibine

Stibine is a powerful haemolytic agent. There is limited data available on the toxicity of stibine following acute exposure. The toxic effects of acute exposure to stibine are thought to resemble those associated with arsine exposure [5].

Inhalation

Arsine

Symptoms of arsine poisoning develop within 1–24 hours (usually within a few hours) after exposure, depending upon the concentration and duration of exposure [1]. Exposure to 10–32 mg/m^3 of arsine may cause symptoms within a few hours. Symptoms of arsine toxicity have been observed following brief exposure to 100 mg/m^3. A 30-minute exposure to 80–160 mg/m^3 is considered lethal and inhalation of 800 mg/m^3 is instantly lethal [2, 4].

Initial symptoms include headache, malaise, weakness, dizziness, dyspnoea, red staining of the conjunctiva, abdominal pain, nausea and vomiting. Dark red urine due to the presence of haemoglobin generally develops within 4–6 hours post-exposure [1].

Haematological changes reported in humans following acute exposure to arsine include anaemia, leukocytosis, and increased plasma-free haemoglobin, iron and potassium concentrations. Damage to red blood cells (such as basophilic stippling, Heinz bodies, anisocytosis, poikilocytosis, red blood cell fragments and ghost cells) may also be observed [1, 6].

Renal failure secondary to haemolysis, if left untreated, is often the cause of death following arsine exposure. In severe cases oliguria or anuria may develop within 2 days after exposure [1]. Free haemoglobin, erythrocytes, proteins, casts and methaemoglobin have been found in the urine of individuals acutely exposed to arsine [1, 4].

Jaundice of the skin and mucous membranes is observed at 24–48 hours following exposure [1]. Serum bilirubin and lactate dehydrogenase levels are usually elevated and the liver is often enlarged and tender. However, severe liver damage has rarely been reported following arsine exposure [6].

Toxic pulmonary oedema or acute circulatory failure has been reported as the cause of death in some cases of arsine poisoning. Tachycardia and ECG abnormalities, including alterations in the S-T segment and elevation of the T-wave, have been reported [1, 2, 7]. In some cases, ECG abnormalities have lasted for several months after exposure [1, 4].

Stibine

Several cases of poisoning have been reported following occupational exposure to a mixture of gases including stibine. Headache, nausea, weakness, abdominal and lumbar pain, haematuria and haemolytic anaemia were observed in workers exposed to a mixture of stibine, arsine and hydrogen sulphide [5].

Delayed effects following an acute exposure

Arsine

Peripheral neuropathy may develop over the first few months following exposure to arsine [2]. Neuropsychological symptoms including irritation, confusion, memory loss, agitation and disorientation have also been reported in individuals acutely exposed to arsine [1]. Vertical white lines on the nails (Mee's lines) may appear 2–3 weeks after exposure [6].

Animal and in-vitro data

Inhalation

Arsine

LC_{50} (10 minute) values have been reported as 390, 250, and 650 mg/m^3 in the rat, mouse and rabbit, respectively. The 50-minute and 24-hour LC_{50} were 100 and 25 mg/m^3, respectively, in the mouse [1].

In an arsine lethality study LC_{50}s of 898, 577 and 146 mg/m^3 were reported in rats exposed for 30 minutes, 1 hour and 4 hours, respectively. Rats in the group exposed for 30 minutes generally died within 3 days following exposure. Dyspnoea was observed during exposure and a concentration-related increase in haematuria was recorded post-exposure [8].

Stibine

In an acute inhalation study rats and guinea pigs were exposed to 1395 or 799 mg/m^3 antimony as stibine, for 30 minutes. Renal tubular dilation was observed in the rats and guinea pigs exposed to 799 mg/m^3 antimony as stibine. Exposure to 1395 mg/m^3 antimony as stibine resulted in the development of pulmonary oedema and death [9].

Health Effects of Chronic/Repeated Exposure

Human data

There is no data on the effects of chronic exposure to stibine in humans or animals. The following sections cover arsine only.

Inhalation

The effects of chronic exposure to arsine are similar to those observed following acute exposure. The main difference from acute exposure is the longer period of latency [1, 4]. The symptoms of chronic arsine inhalation include shortness of breath on exertion, malaise, headache, nausea, anorexia, paresthesia and muscle pain. Peripheral neuropathy, liver and kidney impairment, anaemia and basophilic stippling have been reported in individuals occupationally exposed to arsine [1, 4, 10]. In an occupational study the degree of anaemia in workers chronically exposed to arsine was proportional to the duration of exposure to arsine [1, 4].

Genotoxicity

There is currently no data available regarding the genotoxicity of arsine in humans.

Carcinogenicity

There are no studies in the literature regarding the carcinogenicity of arsine per se [1]. Arsine is, however, metabolised to inorganic arsenic compounds which are recognised human carcinogens (IARC Group 1) [11].

Reproductive and developmental toxicity

There is limited data on the reproductive and developmental effects of arsine in humans. A few occupational studies have reported an increase in the rate of miscarriage among women who work in the semiconductor industry, where arsine is used to produce microchips [2, 10, 12]. The studies had several limitations, including small sample size and exposure to multiple chemicals. Therefore, it was not possible to determine the role of arsine in the observed increase in rate of miscarriage [12, 13].

Animal and in-vitro data

Inhalation

Repeated exposure studies in the rat, mouse and hamster have indicated that there were no quantitative differences in the toxic effects seen. The most sensitive endpoint related to effects on the haematopoietic system namely haemolysis, abnormal red blood cell morphology and increased spleen weight (due to increased removal of damaged red blood cells and increased splenic haematopoiesis).

In hamsters, a significant increase in relative spleen weight was noted following exposure to ≥8.1 mg/m^3 arsine, 6 hours a day, 5 days a week for 28 days [1, 10]. A number of studies

have reported increases in spleen weights in rats and mice exposed to arsine concentrations of 0.08 mg/m^3 and above, 6 hours a day for up to 13 weeks [10]. Anaemia (reduced haemoglobin, haematocrit, red cell count) was reported in rats and mice exposed to arsine concentrations of 1.6 mg/m^3 and above, 6 hours a day, 5 days a week for up to 90 days [1].

Increased susceptibility to bacterial infection and a reduction of T-lymphocytes in the spleen were observed in mice exposed to 1.6, 8.1 and 16 mg/m^3 arsine, 6 hours a day for 14 days [10].

Genotoxicity

There is currently no data available regarding the genotoxicity of arsine.

Carcinogenicity

There is currently no data available regarding the carcinogenicity of arsine.

Reproductive and developmental toxicity

There is limited data on the reproductive and developmental effects of arsine in animals.

In an inhalation study rats and mice were exposed to 0.08, 1.6 or 8.1 mg/m^3 arsine, 6 hours a day, on gestation days 6 to 15. In mice, the dams exposed to 8.1 mg/m^3 had significantly enlarged spleens, but no developmental toxicity was observed. In rats, the dams exposed to 8.1 mg/m^3 arsine also had significantly enlarged spleens and a significant increase in fetal body weight was observed. Increasing fetal liver concentrations of arsenic were observed with increasing maternal exposure. No other developmental or reproductive effects were noted [10, 12, 13].

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This document from the PHE Centre for Radiation, Chemical and Environmental Hazards reflects understanding and evaluation of the current scientific evidence as presented and referenced here.

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