Arsenic trioxide

CAS: 1327-53-3
MF: As_2O_3
MW: 197.8
Solubility: low solubility in water (37 g/l at 20°C, 115 g/l at 100°C); slightly soluble in alcohol; soluble in dilute HCl solution [1].

As^{3+}
MW: 74.92

Major uses
Arsenic trioxide is used for manufacturing of other arsenic compounds which are ingredients in insecticides, herbicides, and fungicides. It is also used as a wood preservative, in metallurgical processes, in the manufacture of glass and ceramics, in pharmaceutical preparations, in textile industry etc. [1, 2].

Human toxicity
Arsenic trioxide is a very toxic compound at oral ingestion, skin contact, and inhalation of its dust. Potentially fatal doses have been listed as 70 to 180 mg, or 1 to 4 mg/kg, respectively [3]. The minimum oral lethal dose was estimated as 120 mg [2].

At an acute ingestion of arsenic trioxide, nausea, vomiting, diarrhea, and abdominal pain are early symptoms occurring within 30 min to several hours. Primary target organ is the gastrointestinal tract (GIT), where hemorrhagic gastroenteritis can occur in serious cases. Among cardiovascular symptoms are tachycardia, ventricular fibrillation, and heart failure described. Neurological symptoms can include peripheral neuropathy which is damage to the peripheral nervous system (PNS), toxic delirium, encephalopathy (cerebral edema), headache, hallucinations, seizures, and coma. Hepatotoxicity and nephrotoxicity were also reported [1, 2].

Arsenic (As^{3+}) is a trace element that is present in all human tissues, probably bound to protein. In blood, it is evenly distributed between plasma and erythrocytes. Blood concentrations in normal subjects found to range 0.003-0.005 mg/l in four U.S. communities [4]. An arsenic blood level below 0.007 mg/l is considered in the normal range [2]. Average clinically monitored (8 cases) lethal blood concentration of arsenic was found to be 7.6 mg/l [5]. Mean acute lethal serum concentration, based on data from three handbooks, was 2.5 mg/l [6].

OSHA PEL (permissible exposure level): 10 $\mu g/m^3$ (averaged over an 8-h workshift) [2].

Carcinogenicity: arsenic trioxide is carcinogenic to humans. There is strong epidemiological evidence of carcinogenicity in occupationally exposed workers, such as an increased frequency of lung cancer, bladder, kidney, prostate, liver, breast, skin and colon cancer. Carcinogen rating 1 (IARC, 2004); Class A (EPA, 2004) [2].

Kinetic data
Absorption: dissolved arsenic trioxide is easily absorbed from GI. Inhaled fine dust may be absorbed directly; absorption through the skin is also possible [2].

Distribution: after uptake into the bloodstream, arsenic is distributed intracellularly in all organs. The highest concentrations have been found in liver, kidneys, spleen and heart [4].

Kinetic: biphasic at the overdose situation [6].

Arsenic crosses the placenta and has resulted in neonatal death [2].

Eliminarion half-life in blood: the initial (biological) phase is short (1 to 2 h); second phase, at the overdose situation may be up to 30 h [6].

Blood protein binding: probably bound, but exact data are missing (see Human toxicity).

Passage of blood-brain barrier: restricted [6].

Metabolism and excretion

Trivalent arsenic is metabolized, primarily in the liver, to the non toxic compounds. The major form of arsenic in urine after ingestion of arsenic trioxide is dimethylarsinic acid (50%) indicating *in vivo* methylation reaction [4, 7]. Other compounds excreted in urine are methylarsonic acid (14%), pentavalent arsenic (8%) and trivalent arsenic (8%) [3].

Excretion is by the kidney; it is nearly complete within 6 days and accounts for over 90% of a dose, mainly via urine. Only a trace amount is excreted in the feces (reviewed in [4]).

Toxicological mechanisms

Arsenic is cytotoxic for all cells. It affects mitochondrial enzymes and impairs tissue respiration. It was proposed that in mitochondria arsenic competes with phosphate during oxidative phosphorylation, and also that it inhibits of energy-linked reduction of NAD (reviewed in [7]).

The toxic effects caused by acute exposure to arsenic trioxide are due in large part to its ability to bind to cellular proteins containing sulfhydryl groups. This inhibits the production of energy needed to maintain tissue functions, and results in a decrease in glutathione, which is necessary for the metabolic detoxification of arsenic [1].

The lethal mechanisms are multisystem failure due to uncoupling of oxidative phosphorylation and inhibition of pyruvate and succinate oxidative pathways [6, 7].

Target organs: The primary target organs are the GIT, heart, brain and kidney. The PNS, skin, and bone marrow are also affected [2, 6]. Arsenic trioxide has direct toxic effects on endothelial cells, increasing the permeability of small blood vessels [1].

References

1. ATSDR, Agency for Toxic Substances and Disease Registry (2005) Google, via internet.
2. Poisindex, Thomson Micromedex (2005).
3. Haddad, L.M., Winchester, J.F. (1990) *Clinical Management of Poisoning and Drug Overdose*. 2nd ed., pp. 1024-1034. W.B. Saunders Company.

4. Baselt, R.C. & Cravey, R.H. (1995) *Disposition of Toxic Drugs and Chemicals in Man*. 4th edn., pp 56-60. Chemical Toxicology Institute, Foster City, CA, USA.
5. Hallander, S., Bondesson, I., Clemedson, C., Löving, T., Sandler, H., Ekwall, B. (1995) *MEIC Monography: Arsenic.* http://www.cctoxconsulting.a.se/26_arsenic.pdf
6. Ekwall, B., Clemedson, C., Crafoord, B., Ekwall, Ba., Hallander, S., Walum, E., Bondesson, I. (1998) MEIC evaluation of acute systemic toxicity. Part V. Rodent and human toxicity data for the 50 reference chemicals. ATLA 26, 571-616.
7. *Casarett and Doull's Toxicology (The Basis Science of Poisons)* (1986) Klaassen, C.D., Amdur, M.O., Doull, J., eds., pp. 588-591, Macmillan Publishing Company.

Written by Ada Kolman, December 2005; revised March 2007
ada. kolman@telia.com