LEARNING TOXICOLOGY THROUGH OPEN EDUCATIONAL RESOURCES

Arsenic

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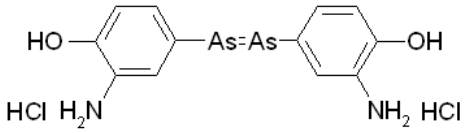
ARSENIC *(Lat. arsenicum, As)*

= natural element

1. Uses:

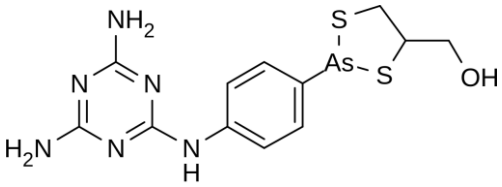
- industrial manufacturing processes, computer industry (semiconductors indium arsenide, galium arsenide)
- metals processing - e.g. arsenical pyrites FeAsS
- burning fossil fuels
- ingredient in insecticides, rodenticides, weed killers (e.g. calcium and magnesium arsenate)
- wood preservation (chromium - copper - arsenate)
- manufacturing of pigments for paints, ceramics, glass
- Drugs: ***in the past*** - treatment of syphylis and psoriasis

1910 - Arsphenamine (Salvarsan®) - discovered by Paul Erhlich. This compound was the first modern chemotherapeutic agent, used for the treatment syphilis.



1800 – Fowler´s solution (1% potassium arsenite) – tonic, aphrodiasic and an appetite stimulant

Drugs ***today:*** melarsoprol - treatment of African sleeping sickness



As_2O_3 (Trisenox®) - chemotherapeutic agent for acute promyelocytic leukemia

Arsenic trioxide (As_2O_3) was in the past a popular poison

→ nicknames: THE KING OF POISON, INHERITANCE POWDER

16th and 17th centuries: the most famous arsenic poisoners were in Italy the Borgias family and lady Toffana – a professional poisoner or in the French royal court a woman called La Voisin.

Arsenical powder was used for removing rivals, husbands, for political assassination, solutions inheritance disputes …

As_2O_3 has some ideal properties: it is tasteless, odorless and colorless. Moreover, the lethal dose (LD) for men is relatively low: about 200mg

Arsenic poisoning was often undetected in the past because it had many similar symptoms to cholera which was quite common at that time.

2. Types of arsenic compounds:

The toxicity of As depends on the valency and the type of compound.

Valency:

The arsenic atom exists in the elemental form and in trivalent and pentavalent oxidation states.

Type of compound:

inorganic arsenicals (white arsenic, and the arsenate AsO_4^{3-} and arsenite AsO_3^{3-}salts)

Organic arsenicals (trivalent and pentavalent) **+ Arsane (arsine gas, AsH_3)**

Elemental arsenic is considered to be nontoxic, because it is insoluble.

Tab.1: As compounds and toxicity

As compounds: decreasing order of toxicity
Arsane AsH_3
Arsenites, arsenic trioxide As^{3+}
Arsenates As^{5+}
Elemental arsenic As^0

Inorganic As^{3+} compounds are more toxic than organic As^{3+}

Toxicity increases in the sequence of organic arsenicals < As^{5+} < As^{3+} < arsane (AsH_3). The organic arsenicals usually are excreted more rapidly than are the inorganic forms. The pentavalent arsenicals have very low affinity for thiol groups, in contrast to the trivalent compounds, and are much less toxic.

The most toxic are compounds containing trivalent arsenic.

A gaseous compound named arsane (AsH_3) is the most toxic As compound. It produces toxic effects that are distinct from those of the other arsenic compounds.

3. Mechanism of toxic action:

As^{3+} has high affinity to –SH groups of cellular enzymes

→ decreased production of acetyl coenzyme A (= essential cofactor in the ATP - generating Krebs cycle).

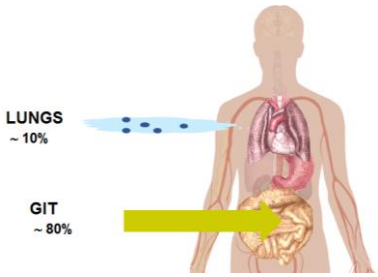
As^{5+} has a molecular structure similar to that inorganic phosphate, it can substitute for phosphate in processes cellular respiration. High energy phosphate bonds are not made → uncoupling of oxidative phosphorylation.

4. Toxicokinetics:

Absorption:

Inorganic arsenic compounds

are mainly absorbed in the GIT (80%) and the lungs (10%)



Distribution:

After absorption, rapidly distribution in the blood (binding to the hemoglobin).

Within 24 hour redistribution: in the liver and kidneys

Within 2 - 4 weeks redistribution: in the hair and nails (= keratin is rich for –SH groups)

Arsenic readily crosses the placental barrier and fetal damage has been reported. It does not readily penetrate blood-brain barrier.

Biotransformation:

Inorganic As^{3+} compounds are methylated to form the less toxic compounds.

Methylation is age dependent (chidren methylate faster).

As^{5+} are converted to the more toxic As^{3+} prior to the methylation.

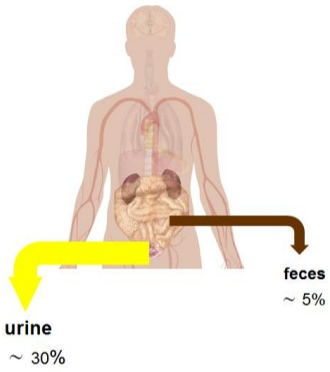
Excretion:

The major route of arsenic elimination is through the kidney.

Urinary arsenic excretion is rapid (30% of arsenic is eliminated within 24 hours).

Small amounts are excreted in feces, sweat, breast milk.

High concentrations of arsenic are found in hair and nails.



5. Intoxication:

Acute effects:

Tab.2: **Acute p.o. intoxication**

Clinical features	As_2O_3 -- LD 200mg
GIT	metallic taste in the mouth, vomiting (sometimes bloody), gastroenteritis:severe gastric pain, rice - watery diarrhea, dehydratation
cardiac	circulatory insufficiency and anuria
neurologic	paresthesia, CNS depression, coma

Death from acute arsenic poisoning is usually caused by **irreversible circulatory insufficiency.**

Chronic effects:

The contamination of groundwater in Bangladesh = the largest poisoning of a population in history with millions of people exposed

WHO recomended - 10µg/l in drinking water

Well water in Bangladesh - >50µg/l

Groundwater used for drinking – contaminated with naturally occuring inorganic arsenic

Share video: *https://www.youtube.com/watch?v=W3Hvexu5SqM*

The apperance of Mees´ lines in fingernails is a characteric feature of arsenic poisoning:

Tab.3: **Chronic p.o. intoxication**

Clinical features		
Cutaneous		hyperkeratosis, hyperpigmentation of the palms and soles, cancer
Neurologic		peripheral neuropathy, encephalopathy
Gastrointestinal		diarrhea, jaundice and liver cirrhosis

Tolerance to As can develop:

There are so called „arsenic eaters", that survived large dose od arsenic:

e.g. peasant from Styrian Alps ate 400 mg of arsenic without signs of toxicity.

Carcinogenesis and teratogenesis.

IARC has classified As as a known human carcinogen (skin, lung, kidney, liver, prostate cancer).

6. Laboratory determination:

Acute intoxication: most of As is completely excreted within 3 days.

As concentration in urine is valuable indicator of As poisoning but because of rapid excretion, a sample should be ideally collected within 24 h hours after intoxication.

Attention: ingestion of seafood (contain large amount of nontoxic arsenobetaine and arsenocholine) can „falsely" elevate total urinary arsenic.

Blood levels: are highly variable

Nails and hair: elevated concentrations persist for months after urine levels normalize = indicator for chronic exposure.

It was difficult to detect arsenic in tissues of victim in the past.

First forensic toxicology test *→ 1836*

James Marsh *(British chemist) developed a method for detecting As in human body.*

The sample containing As_2O_3 *was combined with Zn and* H_2SO_4*, which produces arsine gas (*AsH_3*).* AsH_3 *was led through heated glass tube and was deposited as a mirror in a cold surface of the tube.*

The Marsh test is highly sensitive even to small concentrations of arsenic.

Share video: *https://www.youtube.com/watch?v=-vUZdAwgl2g*

Was Napoleon Bonaparte poisoned?

In Napoleon´s hair arsenic was detected → suspicion, that he was poisoned. Napoleon Bonaparte was not deliberately poisoned by his enemies, but he was chronically exposed to As from air. Wallpaper and draperies in his house on the island of St. Helena were coloured with As containing pigment (Scheele´s green dye - copper arsenite). However, this dye released a volatile form of arsenic, methylarsine in damp condition and in the presence of mold and microorganisms.

7. Treatment of arsenic poisoning:

Chelatation therapy.

The recommended antidotes are:

- ***Dimercaprol*** (=dimercaptopropanol = British antilewisite = BAL) contains thiol groups that compete with endogenous -SH for arsenic
- DMPS = ***dimercaptopropane sulfonate*** – binds arsenic to form a stable five-membered ring compound (complex As-DMPS), which is more efficiently excreted in the urine

Dimercaprol *(also called* ***B****ritish* ***A****nti –* ***L****ewisite or abbreviated BAL) was secretly developed by british chemists at the Oxford University during the World Was II as an antidote for Lewisite.*

Lewisite *= arsenic based compound which was used as a chemical weapon (it causes blistering of the skin, eyes and respiratory tract) and has been known as the „Dew of Death“.*

Lewisite **=** *2-chlorovinyldichloroarsine*

BAL is currently recommended for the treatment of heavy metal poisoning, especially for As, Au, Hg and Pb.

Share video: *https://www.youtube.com/watch?v=NB-EMz14RuU*

8. Arsane = (arsine gas, arsenous hydride, AsH_3)

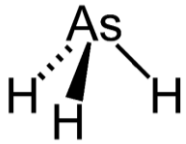
= gas with garlic odor.

In comparison with arsenic trioxide has arsane different toxic effect:

hemolysis followed by hemoglobinuria.

Death often results from renal failure.

Dimercaprol has no effect



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