

ARSENIC TOXICOLOGY

I – Generalities

Physicochemical properties

Metalloid, steel-gray color, garlic odor, very brittle.

Belongs to the pnictogen family, fifth column (Group V A).

Combines with sulfur.

Reacts violently with oxidants including O₂.

Oxidizes in air (at high temperature) forming: As₂O₃ (particles in air).

Atomic mass: 74.92

Melting point: 615°C

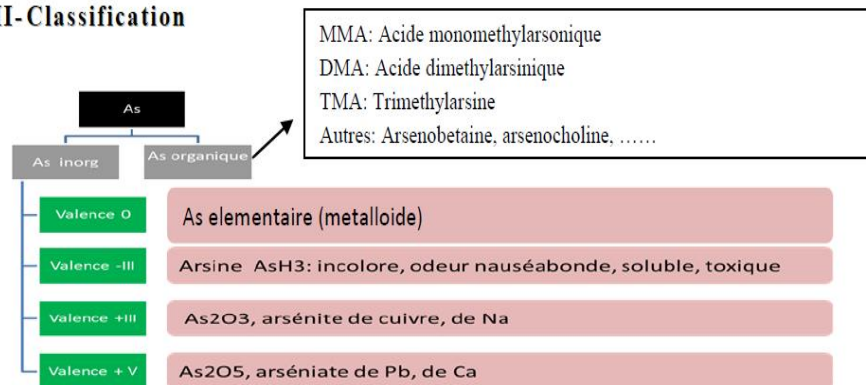
Boiling point: 817°C

Formation of trihalides (at high temperature): arsine, important in determination by hydride generation (FIAS method).

Main minerals

- Realgar (As₄S₄) – red
- Orpiment (As₂S₃) – yellow
- Mispickel (FeAsS)
- Arsenopyrite (FeAs₂)

II- Classification



III – Behavior in the Environment

Depends on: pH, redox conditions, dissolution, methylation, microorganisms, ionic strength (IS), temperature, oxygenation, presence of sediments, etc.

Media – Sources – Behavior

Air:

Volcanoes, industry, combustion, incineration, exhaust gases

- Arsine (As⁻³): volatile gas
- Oxidation of arsine in air into As³⁺ and As⁵⁺ (then deposition)
- Inorganic arsenic (particle form): As₂O₃

Water:

Groundwater, soil leaching, industrial discharge

- Acidic pH, depth, anaerobic conditions → As³⁺
- High ionic strength (salinity) → ↑ As⁵⁺

Soil:

Volcanic rocks, atmospheric fallout

- Retention of As^{5+} (iron, manganese, aluminum hydroxides, clay) in aerobic conditions
- In acidic reducing environment \rightarrow stable As^{3+}

- **IV – Sources of Exposure**

Environmental

- Natural: volcanoes, Bangladesh water
- Anthropogenic: industry, dyes, combustion, insecticides, treated wood

Occupational

- Semiconductor manufacturing plants

Criminal

- Rare poisoning, war gas (arsine)

Others

- Tobacco: 10 μg / 40 cigarettes
- Fowler's solution (no longer used)

Compounds:

- MMA: monomethylarsonic acid
- DMA: dimethylarsinic acid
- TMA: trimethylarsine
- Others: arsenobetaine, arsenocholine
- Elemental arsenic (metalloid)

- **V – Toxicokinetics**

Absorption**Inhalation:**

30–35% (depends on solubility, particle size)

Arsine: passive diffusion in lungs

Ingestion:

90% (As^{3+} , As^{5+})

75–85% (MMA, DMA)

Cutaneous:

Low and negligible except damaged skin (Lewisite)

Distribution

- Bound to plasma proteins, hemoglobin (RBC), metallothionein
- Half-life: 1 hour
- Organs: liver (As^{3+}), kidneys, lungs, muscles, skin, appendages
- Crosses placenta and milk

Arsine: binds RBCs, oxidized then transported to liver

- Plasma
- Half-life: 5–20 hours
- Distributed in soft tissues
- Crosses blood-brain barrier

Metabolism

1. Oxidation: $\text{As(III)} \rightarrow \text{As(V)}$
2. Reduction: $\text{As(V)} \rightarrow \text{As(III)}$
 - Enzyme: arsenate reductase
 - Coenzyme: GSH
3. Sequential methylation
 - Enzyme: methyltransferase
 - Coenzyme: SAM (S-adenosylmethionine) – CH_3 donor

Limited to 0.2–1 mg/day

- ↓ metabolism in hepatic insufficiency, ↓GSH, ↓ CH_3 donors (malnutrition)
- Depends on exposure type (acute, chronic)
- Detoxification role debated (toxic intermediates produced)

Elimination

- Urinary: 45–85% (recent exposure)
- Depends on species, exposure type, nutrition, pathology
- Half-life: 40–60 hours

Also:

- Breast milk
- Bile (bound to GSH)
- Hair and nails (chronic exposure)

• VI – Mechanisms of Toxic Action

Biotransformation

Reactive, genotoxic, carcinogenic products

1. Oxidative Stress (As^{3+} , As^{5+} , organic As)

- ROS formation: inhibition of antioxidant enzymes, affinity for GSH
- H_2O_2 production during $\text{As}^{3+} \rightarrow \text{As}^{5+}$
- Iron release \rightarrow Fenton reaction $\rightarrow \text{OH}\cdot$
- $\text{DMA}^{3+} \rightarrow$ dimethylarsine \rightarrow reacts with $\text{O}_2 \rightarrow$ peroxy radicals
- Inhibition of respiratory chain $\rightarrow \downarrow \text{ATP}$

\rightarrow Increased GSH synthesis

\rightarrow Induction of stress proteins (HSP, MT)

\rightarrow Altered signaling pathways (\downarrow NO synthase)

$\rightarrow \downarrow$ vascularization \rightarrow Black foot disease

\rightarrow DNA damage

2. Genotoxicity

(Mainly MMA, DMA, TMA)

- DNA strand breaks, Base oxidation, Chromosomal aberrations
- DNA methylation
- Clastogenic and aneugenic effects
- Gene amplification
- p53 suppression
- Proliferation stimulation (c-myc, c-fos)

3. Interference with Energy Metabolism

As³⁺:

- Inhibits lipoic acid
- Inhibits pyruvate dehydrogenase

As⁵⁺:

- Phosphate analog
- Formation of unstable arsenate esters
- Uncoupling oxidative phosphorylation
- Replacement of phosphate in Na⁺ pump

4. Action on Thiol Groups (-SH)

- Enzyme inhibition
- P450 inhibition (As³⁺)
- ↑ MAO, cytochrome oxidase
- ↓ phosphatase, ACE

Other effects

- Steroid metabolism alteration
- ↑ testosterone, progesterone metabolism

Heme metabolism:

- ↑ porphobilinogen deaminase
- ↑ uroporphyrinogen decarboxylase
→ uroporphyrinuria, coproporphyrinuria
- ↓ ALA synthase, ↓ heme synthase

- **VII – Acute Toxicity**

Ingestion**LD₅₀:**

- As₂O₃ = 2 mg/kg
- NaAs = 0.325–0.54 mg/kg
- MMA = 793 mg/kg
- DMA = 77 mg/kg

Clinical signs

- Digestive: vomiting, diarrhea (rice-water stools)
- Cardiovascular: hypotension, tachycardia, shock
- Neurological: confusion, coma
- Skin: rash, exfoliative dermatitis

Inhalation**LC₅₀:** 10–250 ppm

- Respiratory irritation
- Cyanosis
- Eye irritation
- Neurological symptoms
- Delayed digestive disorders

Treatment

- Gastric evacuation + magnesium suspension
- Symptomatic (fluids, cardiac support)
- Maintain diuresis, dialysis if needed
- Chelators: BAL, DMPS, DMSA, penicillamine
- Exchange transfusion if severe

- **VIII – Chronic Toxicity**

Skin

- Erythema, ulceration, pigmentation
- Hyperkeratosis (palmar)
- Bowen's disease → skin cancer

Other signs

- Mees lines (nails)
- Hepatic: hepatomegaly, fibrosis
- Neuropathy (sensory + motor)
- Renal: proteinuria, ↑ creatinine
- Cardiovascular: arrhythmias, QT prolongation
- Raynaud disease, Black foot disease
- Hematological: anemia, leukopenia
- Reproductive toxicity

Cancer

Skin, liver, lung, kidney, bladder (Group 1 carcinogen)

- **IX – Analysis**

Samples: Blood, urine, tissues, hair, nails

Mineralization: Acid digestion (HNO_3 , H_2SO_4)

Methods

- Colorimetry
- Polarography
- Voltammetry
- Atomic absorption spectrometry (FIAS)
- HPLC, GC
- X-ray fluorescence
- Neutron activation

Biomarkers

- Blood: recent exposure
- Urine: As^{3+} , As^{5+} , MMA, DMA
- Hair/nails: chronic exposure

Standards

- Drinking water: 10 $\mu\text{g}/\text{L}$
- Air: 1 $\mu\text{g}/\text{m}^3$
- Occupational air: 0.2 mg/m^3
- Urine: 50 $\mu\text{g}/\text{L}$