

Chemical Toxicology

- Toxicology : science of poisons.
- "study of the adverse effects of chemicals or physical agents on living organisms"
- historical developments of toxicology began with early cave dwellers who identified the poisonous plants and animals and used their extracts for hunting or in warfare.
- "all substances are ~~potent~~ poisonous, there is none which is not a poison. The right dose differentiates a poison from a remedy."

Toxicology Terminology

~~POTENT~~ TOXIC: poisonous or deadly effects on the body by inhalation, ingestion, or absorption, or direct contact with a chemical.

~~TOX~~

TOXICANT: anything that can produce an adverse biological effect. maybe chemical, physical, or biological in form.

For ex: CN (chem), radiatⁿ (physical), snake venom (biol)

TOXIN: toxic substance produced naturally.

- poisonous substance of microbial (bacteria or the other tiny plants & animals), vegetable, or synthetic chem. origin that reacts with specific cellular components to kill cells, alter growth or dev, or kill the organism.

TOXICITY: the degree to which a substance is ~~is~~ poisonous or can cause injury.

- TRADITIONAL METHOD: count how many orgn. die or suffer when exposed to various conc. of substn.

a. acute toxicity - rapid development of symptoms, immediate harmful effects generated by intake of high doses of the toxicity.

b. chronic toxicity - harmful effects of long-term exposure to relatively low doses of toxicants.

ex: Pb or Hg poisoning, cancer.

TOXIC EFFECTS: health effects that occur due to exposure to a toxic substance; poisonous effect on the body.
Lethal - resulting in death

Sublethal - not directly resulting in death

• acute effect: CO and CN poisoning

→ sudden and severe exposure and rapid absorption of the substance.

→ adverse effects are often REVERSIBLE. (short time period)

• chronic effect: Pb or Hg poisoning

→ by prolonged or repeated exposures of long duration.

→ are often IRREVERSIBLE. (long periods of time)

• local effect: strong acids or alkalis.

→ adverse health effect that takes place at point or area of contact (skin, respiratory tract, eyes, etc.)

→ Absorptn doesn't necessarily occur.

• systematic effect: As, C₆H₆ ~~hematologic system~~,

→ takes place at a location distant from the body's initial point of contact.

→ As: blood, liver, kidney, skin & nervous system

→ C₆H₆ Benzene: affects bone marrow.

- cumulative poisons : heavy metals
 - materials that tend to build up in the body as a result of numeric chronic exposures.
 - effects not seen until adverse health effects occur
- synergistic effect : exposure to alcohols, chlorinated solvents, or smoking and asbestos.
 - when 2 or more hazardous materials are present at the same time, the resulting effect can be greater than the effect predicted based on additive effect of individual subst'.
 - POTENTIATING EFFECT.

DOSE: actual amt. of a chemical that enters the body.

- maybe due to acute or chronic exposure
- toxic effect determined by - amt. of exposure & type.

RESPONSE: any biological effect caused by exposure

XENOBIOTIC: foreign substance ~~found~~ taken into the body.

- may produce beneficial effects (pharmaceuticals) or may be toxic (Pb)

TARGET ORGAN: organ that is damaged by xenobiotic or its metabolism.

SELECTIVE TOXICITY: species differences ~~in~~ in toxicity b/w 2 species simultaneously. It means that chemical will produce injury to one kind of living matter without harming another. (pesticides and drugs)

- insecticide: lethal to insects w/ to animals
- antibiotics: toxic to micro-organisms, non-toxic to humans

SENSITIVITY: Some are sensitive to a certain drug, while others may not be affected. Includes character such as age, sex, inherited traits, diet, pregnancy, state of health, use of medication, drugs or alcohol.

CHEMICAL INTERACTIONS.

Interaction: effect one chemical has on the toxic effect of another chemical.

- drinking water: pesticides, heavy metals, solvents etc.
- air: mix of chemicals (automobile exhaust & smoke)
- influenza treatment: aspirin, antihistamines, cough syrup
- gasoline vapour: 40-50 chemicals mixed.

Types

ADDITIVITY: ~~one~~ Chem A + Chem B → response is combination of both responses A & B

ANTAGONISM: chem A reduces effect of chem B
(antidote) (poison)

POTENTIATION: chem A increases activity of chem B.
chem B has no activity if present alone.

example: Hepatotoxicity by CCl₄ (Drug A) increased by presence of isopropanol (Drug B)

SYNERGISM: chem A drastically increases activity of chem B.
example: lung cancer caused by air pollution, smoking

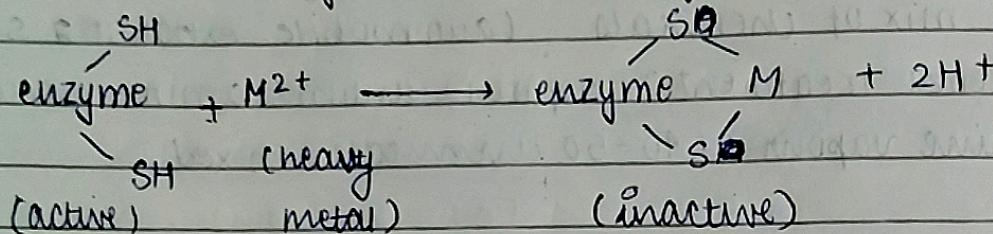
~~PHYSIOLOGICAL DAMAGE~~: ~~reversible~~ → irreversible
 (sulphydryl)
 → -SH, -NH₂,
 -COOH, OH,
 -CONH₂ (amide)

IMPACT OF TOXIC METALS ON ENZYMES

all enzymes are proteins

→ made up of amino acids

1. Inactivation of enzyme in body.



2. Damage to cell membranes

3. Damage to mechanical membranes, leading to inhibition of ATP formation in cell.

4. S-amino levulinic acid dehydrates enzymes involved in Haemoglobin. → inhibited by Pb⁺²

HEAVY TOXIC METAL IDN

→ density more than H₂O

→ Cd, Cr, Hg, Pb, As

Fe level low in blood ↓ = anaemia

Fe level high in blood ↑ = polycythaemia

WHO = World Health Organisation

USEPA = US Environmental Protection Agency

HEAVY METALS

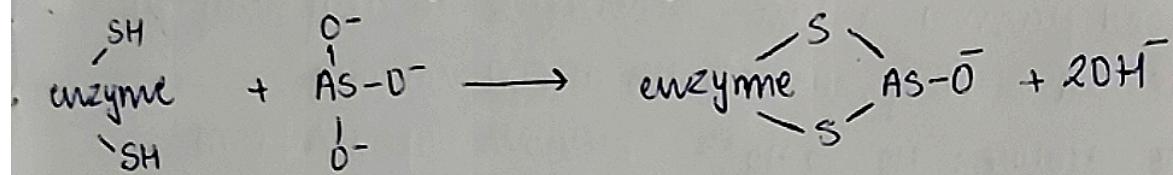
As, Hg, Pb, Cr, Cd

ARSENIC (As)

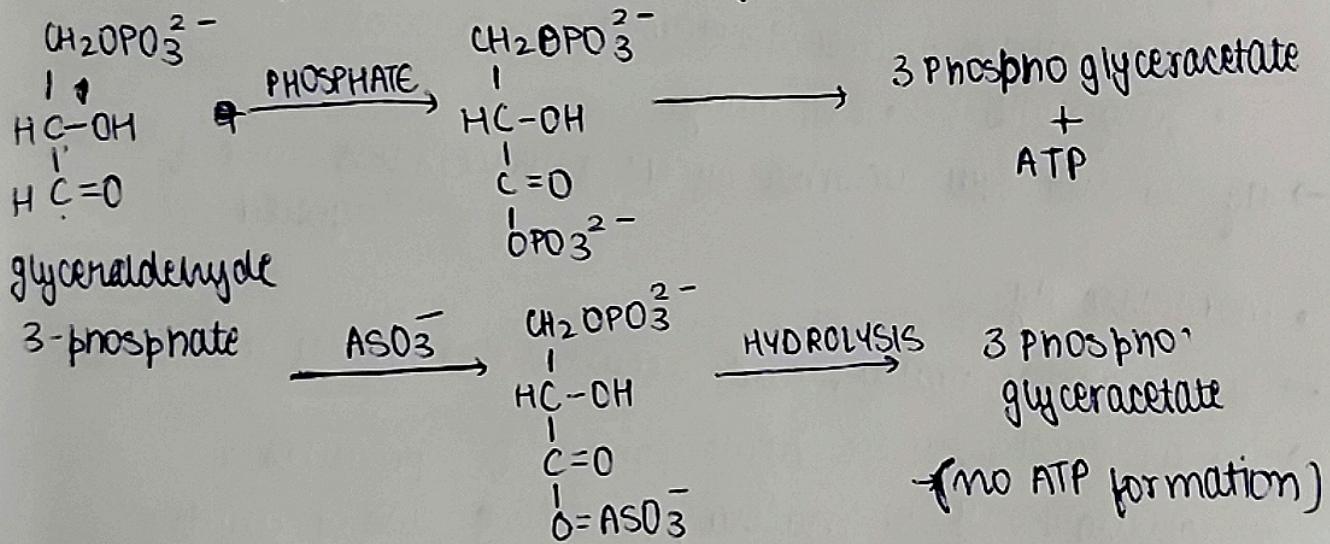
{ As⁰ : metalloid arsenic
As⁺³ : Arsenite trivalent (HIGHLY TOXIC)
As⁺⁵ : Arsenite pentavalent

BIOCHEMICAL EFFECTS

- inhibition of enzyme activity



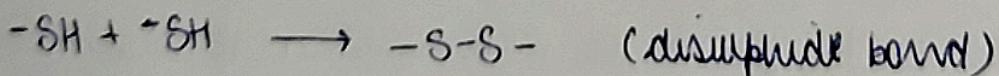
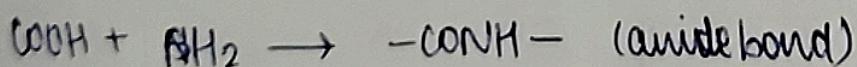
- uncoupling of oxidative phosphorylation



- coagulation of proteins

→ change in structure of protein

↪ loss of enzyme activity → loss in functions



MERCURY (Hg)

{ metallic Mercury (lq form, easily evaporates)
Inorganic Mercury (salt form, highly toxic, corrosive)
Organic Mercury (TOXIC)

BIOCHEMICAL EFFECTS

• Elemental / Metallic Mercury

- absorbed through inhalation. From lungs dissolves into blood plasma & can now diffuse to any body cell.
- inside cell of body, Hg vapours aren't harmful.

enzyme catalyse: $Hg \rightarrow Hg^{+2}$ (prevents vapours from entering the brain)

- Hg^{+2} reaches brain (if)

- Mad hatters disease (exethism) • tremors
- gingivitis • excitability.

- Hg is not well absorbed by GI & hence is less toxic if ingested

• Inorganic Hg

- gains access orally, and accumulates mostly in kidneys

- in GI tract, causes acute poisoning, produces a sloughing away of mucosa, producing loss of fluids & electrolytes.

• Organic Hg

- highly lipophilic (high affinity for fat tissues)

thus absorbed completely by the GI tract.

Accumulates in brain, kidney, skin, hair.

- Mono methyl mercury is 100-1000 times more toxic to humans. It affects the nervous system.

LEAD (Pb)

- found naturally in earth's crust
- always found as a compdt & not in elemental form.

BIOCHEMICAL EFFECTS

- haematological system
 - major effect of Pb is on haeme synthesis (oxygen carrying component of Hb)
 - Pb is absorbed in blood plasma & accumulates in tissues in blood 95-99%. Pb is in red cells, where it binds to Hb and other components causing ANAEMIA.
- neurological effects
 - affects CNS. In brain alters function of cellular calcium and ~~other~~ inactivates blood-brain barrier.
 - causes brain EDMA, affects CNS, causing headache, coma, mortality etc.
- renal effects
 - kidney damage b/c of effect of Pb on cellular respiration.
 - irreversible nephropathy.
- other effects
 - INFERTILITY in men, MISCARRIAGE & STILL BIRTH in women.
 - impairs growth hormone in children & results in weakening & abnormal bone growth.

CHROMIUM (Cr)

$\left\{ \begin{array}{l} \text{Cr}^0 \\ \text{Cr}^{3+} \text{ (naturally in environment, reqd. by humans)} \\ \text{Cr}^{6+} \text{ (VERY TOXIC)} \end{array} \right.$

BIOCHEMICAL EFFECTS

- enhances action of insulin (critical for ~~st~~ metabolism and storage of fats, carbs, proteins)
- Cr^{+4} is absorbed more easily than Cr^{+3}
 - inside body $\text{Cr}^{+6} \rightarrow \text{Cr}^{+3}$ in RBCs
 - distributed to many tissues, kidney, muscle & liver
- Transferrin: principle carrier of Cr (protein)
 - movement of Cr from ~~extracellular~~ blood to LMW (r-)
 - binds to glutamyl acid, cystein, (low mol. wght. Cr) glycine, aspartic acid
- Cr then passes through kidney & eliminated through urine

CADMIUM (Cd)

BIOCHEMICAL EFFECTS

- Metallothionein protein binds Cd is generally thought to reduce its toxicity. In liver, it is produced sufficiently to bind.
- From liver, metallothionein bound Cd reaches kidney & gets selectively accumulated.