Metal toxicity

Metal toxicity or **metal poisoning** is the toxic effect of certain metals in certain forms and doses on life. Some metals are toxic when they form poisonous soluble compounds. Certain metals have no biological role, i.e. are not essential minerals, or are toxic when in a certain form. In the case of lead, any measurable amount may have negative health effects. Often heavy metals are thought as synonymous, but lighter metals may also be toxic in certain circumstances, such as *beryllium and lithium*. Not all heavy metals are particularly toxic, and some are essential, such as iron. The definition may also include trace elements when in abnormally high doses may be toxic. An option for treatment of metal poisoning may be chelation therapy, which is a technique which involves the administration of chelation agents to remove metals from the body.

Toxic metals sometimes imitate the action of an essential element in the body, interfering with the metabolic process resulting in illness. Many metals, particularly heavy metals are toxic, but some heavy metals are essential, and some, such as bismuth, have a low toxicity. Most often the definition of toxic metals includes at least cadmium, manganese, lead, mercury and the radioactive metals. Metalloids (arsenic, polonium) may be included in the definition. Radioactive metals have both radiological toxicity and chemical toxicity. Metals in an oxidation state abnormal to the body may also become toxic: chromium(III) is an essential trace element, but chromium(VI) is a carcinogen.

Toxicity is a function of solubility. Insoluble compounds as well as the metallic forms often exhibit negligible toxicity. The toxicity of any metal depends on its ligands. In some cases, organometallic forms, such as methylmercury and tetraethyl lead, can be extremely toxic. In other cases, organometallic derivatives are less toxic such as the cobaltocenium cation.

Decontamination for toxic metals is different from organic toxins: because toxic metals are elements, they cannot be destroyed. Toxic metals may be made insoluble or collected, possibly by the aid of chelating agents, or through bioremediation. Alternatively, they can be diluted into a sufficiently large reservoir, such as the sea, because immediate toxicity is a function of concentration rather than amount.

Arsenic:

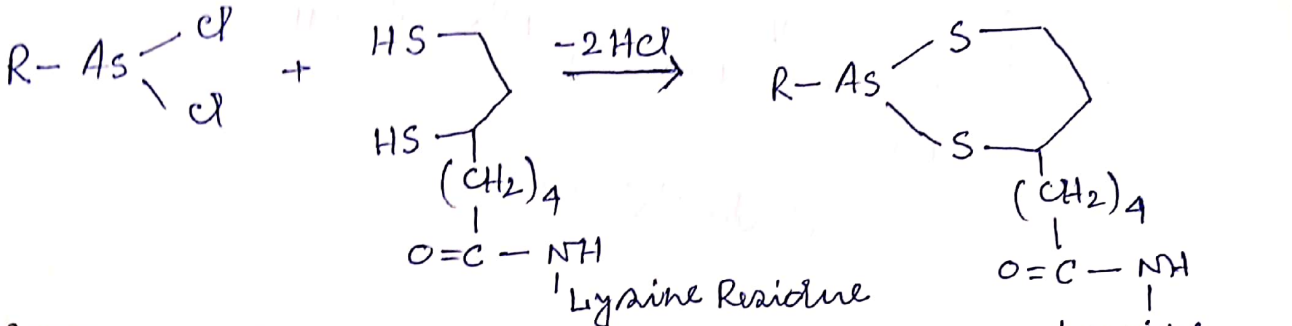
Arsenic, a naturally occurring metalloid and 20th most abundant element in the earth's crust, it ranks highest on the list of hazardous substances toxic to public health. Its existence as elemental, inorganic, and organic in large quantities all over the world makes it one of the most important metals, having adverse effects on the environment and human health. Existing in more than 200 different mineral forms, its availability as arsenate (AsV) accounts for approximately 60%, as sulphide or sulfosalt 20% and the remaining 20% in the form of arsenites, arsenides, oxides, silicates, and elemental arsenic. Volcanic activity, weathering of rocks, geothermal waters, and forest fires constitute some of the natural sources of arsenic. In addition to pollution from natural sources, its applications in animal feed, glass and ceramics, herbicides, pesticides, wood preservatives, metallurgical operations and many others contribute to its anthropogenic pollution. Humans generally encounter arsenic by natural as well as manmade sources through soil, water, air, and food. It is readily found in appreciable concentrations in food items having origin from the sea. Its mere presence in rice, a staple food crop worldwide makes its entry into the human body easier than other sources. Through rice, it poses a greater risk to infants who mainly depend on rice for their meals. As per World Health Organization (WHO) guidelines, a safer limit of 200 µg/kg was established for white rice and a maximum of 400 µg/kg for brown rice. As a group I carcinogen, its contamination of drinking water is a serious environmental calamity worldwide.

In nature, soluble arsenic exists in two common oxidation states, arsenate (AsV) and arsenite (AsIII) present as the oxyanions arsenate (AsO_4^{3-}) and arsenite ($As(OH)_3$), respectively. Following ingestion, it is readily absorbed (>90%) by the gastrointestinal tract. Their toxicities and as such cellular damage vary with respect to their valence states. Difference in their toxicities along with their biological affects arises with respect to their uptake and as such accumulation in the cellular system; *pentavalent arsenicals (AsV) taken up less efficiently show a lower rate of accumulation than trivalent species (AsIII)*. Having greater uptake and high affinity for sulhydryl (–SH) groups of proteins and enzymes, AsIII is considered more toxic than its counterpart, AsV. However, owing to its structural similarity to phosphate, AsV exerts its toxicity through replacement of phosphate in different chemical reactions. As part of their toxicity, AsV replaces the stable phosphodiester bond in ATP, thereby resulting in uncoupling of oxidative phosphorylation events and subsequent depletion

of ATP stores, while depletion of the intermediate of Krebs cycle by AsIII results in the exhaustion of cellular energy via inhibition of cellular respiration.

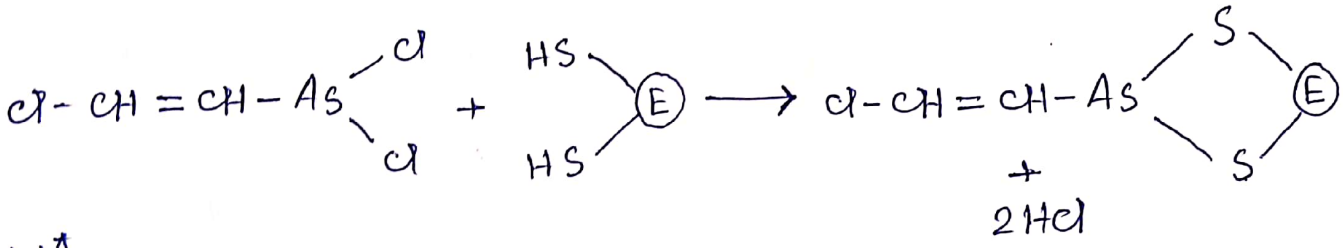
Biological aspects of arsenic poisoning: The compounds containing As(III) are most toxic than As(V). As(III) being soft prfer the –SH groups of different enzymes to inhibit the enzymatic process. It also binds with Keratin disulfides present in hair, nail and skin.

i) Arsenic can show its carcinogenic activity in mouth, esophagus, larynx and bladder, though it can not directly damage the DNA. Probably, As(II) binds with some –SH group containing enzymes which are involved in DNA repair mechanism.



ii) 3-arsonopyruvate [HO-As(O)(OH)-CH_2COCO_2H] can inhibit phosphoenolpyruvate mutase which is required for the biosynthesis of C-P bonds in living bodies.

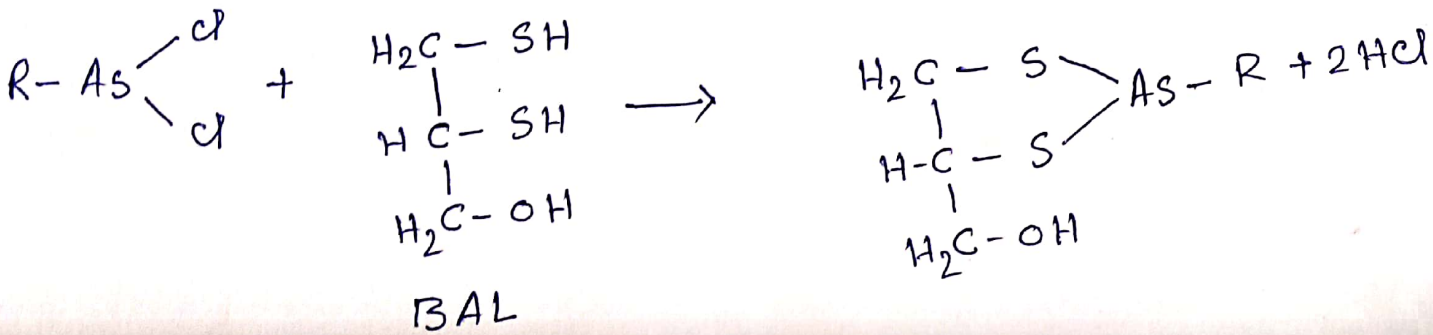
iii) As- compounds can also denature different proteins by attacking the –SH group.



iv)*

Symptoms: Dermatitis, Keratotis, gastroenteritis, Melanosis, Ulceration in limbs, Gangrene and skin cancer.

Detoxification: The recommended chelating antidotes for detoxification of Arsenic are: 2,3-dimercaptopropanol(BAL), D-penicillamine (DPA) etc.



Lead(Pb):

Lead (Pb) is one of the most abundant natural substances on earth. Lead is a highly toxic metal whose widespread use has caused extensive environmental contamination and health problems in many parts of the world. Owing to its physical properties including low melting point and high malleability, it has widespread industrial use. In terms of usage, it ranks fifth on the list of metals. Its use is associated with more than 900 industries, including mining, smelting, refining, battery manufacturing, and so on. In addition to industry, it has applications in fertilizers and pesticide used for agriculture purposes, and in improving the octane rating of gasoline in vehicular traffic systems. As a result of rapid industrialization, increase in the effluent discharge from industrial units located in close proximity to rivers has resulted in an increase in its amount in water bodies. Along with this, application of sewage sludge directly or as part of irrigation from contaminated water bodies, as an exhaust product of leaded gasoline due to increased traffic activities in urban settings and increased use as part of fertilizers and pesticide for agricultural purposes has resulted in the pollution of soils, which has had a serious environmental impact. Together, these (agricultural, industrial, and municipal) activities have resulted in the contamination of groundwater resources. In short, its abundance and widespread usage makes it a well-recognized environmental and occupational toxicant, particularly in the urban environment.

The sources of lead exposure include mainly industrial processes, food and smoking, drinking water and domestic sources. The sources of lead were gasoline and house paint, which has been extended to lead bullets, plumbing pipes, pewter pitchers, storage batteries, toys and faucets (Thurmer *et al.*, 2002). In the US, more than 100 to 200,000 tons of lead per year is being released from vehicle exhausts. Some is taken up by plants, fixation to soil and flow into water bodies, hence human exposure of lead in the general population is either due to food or drinking water (Goyer, 1990). Lead is an extremely toxic heavy metal that disturbs various plant physiological processes and unlike other metals, such as zinc, copper and manganese, it does not play any biological functions. Even at low concentrations, lead treatment was found to cause huge instability in ion uptake by a plant, which in turn leads to significant metabolic changes in photosynthetic capacity and ultimately in a strong inhibition of plant growth.

Toxicity:

i. Lead interferes with the biosynthesis of porphyrin required in Hb synthesis. The enzyme, delta-aminolevulinate dehydrase(ALAD) catalyses the condensation of

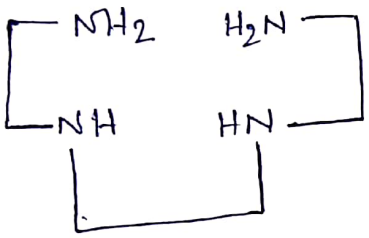
two moles of delta-aminolevilinate(ALA) to form porphobilinogen which act as a building block unit for the synthesis of porphyrin skeleton. Thus lead interacts with the enzyme, delta-ALA dehydrase to inhibit the formation of porphobilinogen.

ii. Pb^{+2} interfere with Ca^{+2} and consequently bones are affected in Pb-poisoning.

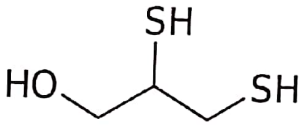
iii. It also damages the liver and gastrointestinal tract.

iv. Pb^{+2} can damage the mitochondria of kidney allowing the loss of glucose, amino acids and phosphate through urine.

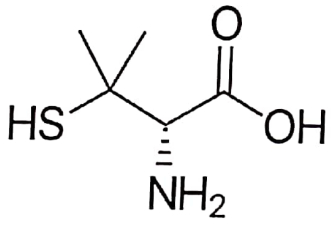
Detoxification: $CaNa_2EDTA$ is used for Pb detoxification. Also DPA and BAL can be used depending upon the condition.



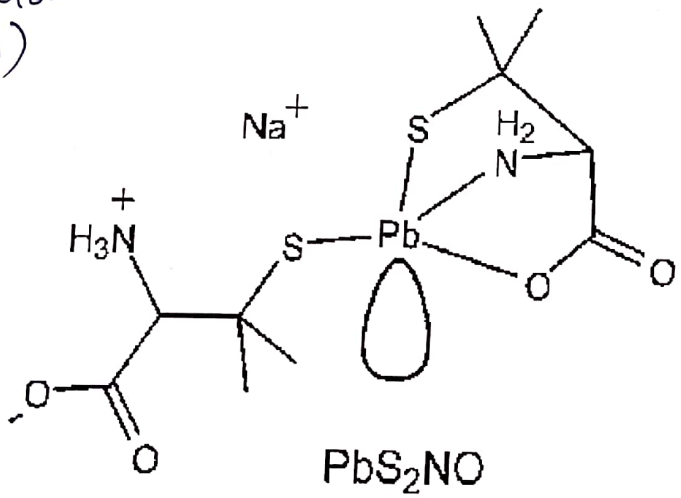
Triethylenetetramine (tsien)



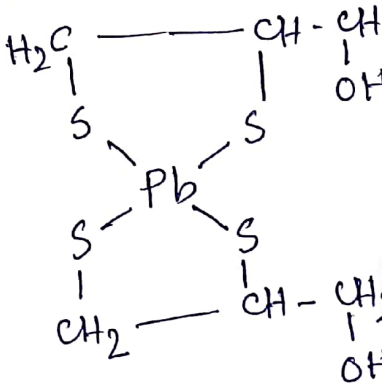
British anti-Lewisite (BAL)



DPA



PbS_2NO



Mercury (Hg):

The metallic mercury is a naturally occurring metal which is a shiny silver-white, odorless liquid and becomes colorless and odorless gas when heated. Mercury is very toxic and exceedingly bioaccumulative. Major sources of mercury pollution include anthropogenic activities such as agriculture, municipal wastewater discharges, mining, incineration, and discharges of industrial wastewater (Chen *et al.*, 2012*). Mercury exists mainly in three forms:*

metallic elements, inorganic salts ($Hg(OH)_2$, $HgCl_2$, CH_3HgCl, $Hg(OH)^+$, $HgCl_3^-$, $HgCl_4^{2-}$ *etc) and organic compound* ($(CH_3)_2Hg$, CH_3Hg^+, *each of which possesses different toxicity and bioavailability.* These forms of mercury are present widely in water resources such as lakes, rivers and oceans where they are taken up by the microorganisms and get transformed into methyl mercury within the microorganism, eventually undergoing biomagnification causing significant disturbance to aquatic lives. Consumption of this contaminated aquatic animal is the major route of human exposure to methyl mercury (Trasande *et al.*, 2005). Mercury is extensively used in thermometers, barometers, pyrometers, hydrometers, mercury arc lamps, fluorescent lamps and as a catalyst. It is also being used in pulp and paper industries, as a component of batteries and in dental preparations such as amalgams. Methylmercury is a neurotoxic compound which is responsible for microtubule destruction, mitochondrial damage, lipid peroxidation and accumulation of neurotoxic molecules such as serotonin, aspartate, and glutamate (Patrick, 2002). Animals which are exposed to toxic mercury have shown adverse neurological and behavioral changes.

Mercury binds to freely available thiols as the stability constants are high (Patrick, 2002). Mercury vapors can cause bronchitis, asthma and temporary respiratory problems. Mercury plays a key role in damaging the tertiary and quaternary protein structure and alters the cellular function by attaching to the selenohydryl and sulfhydryl groups which undergo reaction with methyl mercury and hamper the cellular structure. It also intervenes with the process of transcription and translation resulting in the disappearance of ribosomes and eradication of endoplasmic reticulum and the activity of natural killer cells. The basis for heavy metal chelation is that even though the mercury sulfhydryl bond is stable and divided to surrounding sulfhydryl consisting ligands, it also contributes free sulfhydryl groups to promote metal mobility within the ligands (Bernhoft, 2011).

Toxicity:

i. *Enzyme inhibition*: Both Hg^+ and RHg^+ preferably bind with – SH group of proteins and enzymes. Thus can interact with haemoglobin and serum albumin having –SH groups. CH_3Hg^+ is found to bind with glutathione in red blood cells, so *inhibit the activity of delta-aminolevulinic acid dehydrase and cholin esterase activity.*

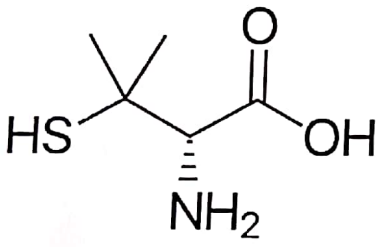
ii. *Hg-C bond is highly stable for a long period in cells and tissues and lipid soluble so it accumulated in the brain tissues.* For fetuses, infants, and children, the

primary health effect of methylmercury is impaired neurological development. Methylmercury exposure in the womb, which can result from a mother's consumption of fish and shellfish that contain methylmercury, can adversely affect a baby's growing brain and nervous system. Impacts on cognitive thinking, memory, attention, language, and fine motor and visual spatial skills have been seen in children exposed to methylmercury in the womb.

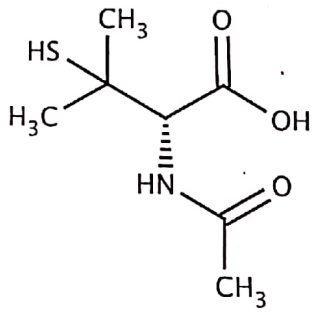
iii. The attachment of toxic specis of Hg with the membrane prevents the active transport of glucose. Thus it can induce neurological problems including mental retardation and cerebral paralysis.

Detoxification:

For detoxification of Hg(II) or $CH_3Hg(II)$ the compound of D-penicillamine(DPA) and its N-acetyl derivative(NAPA), Unithiol etc are used. But NAPA is a better antidote than DPA because of the presence of the lipophilic acetyl group in NAPA.



DPA



NAPA

Cadmium:

Cadmium is a metal of the 20th century. It is a byproduct of zinc production. Soils and rocks, including coal and mineral fertilizers, contain some amount of cadmium.Cadmium has many applications, *e.g.* in batteries, pigments,plastics and metal coatings and is widely used in electroplating (Martin & Griswold, 2009). Cadmium andits compounds are classified as Group 1 carcinogens forhumans by the International Agency for Research onCancer (Henson & Chedrese, 2004). Cadmium can cause both acute and chronic intoxications (Chakraborty *et al.*, 2013). Cadmium is highly toxic to the kidney and it accumulates in the proximal tubular cells in higher concentrations.

Toxicity:

i. Cadmium leads to decalcification in bones and the bones are weakened that they break even on turning in bed.

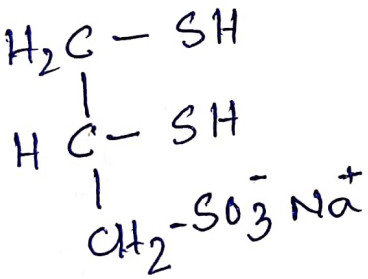
ii. The painfull disease known as *itai-itai* occur due to Cd-content.

iii. Cd-poisoning produces kidney problem. Cd^{+2} being soft prefer the –SH groups. Thus it can inactivate several S-containing enzymes and proteins by blocking –SH groups. In presence of excess amount of Cd^{+2} , Kidney is affected.

iv. Cd^{+2} can substitute Zn^{+2} from several enzymes to produce the toxicity.

Symptoms: The common clinical symptoms in Cd-poisoning are kidney problem, anemia, hypertension, decalcification of bone, glaucoma etc.

Detoxification: To detoxicity of this metal from the body or living system, it requires the Chelation therapy which utilises the administration of some suitable chelating agents to remove the toxic metal. Such chelating agents are $CaNa_2EDTA$, DPA and BAL etc can be used.



Unithiol
(Sodium 2,3 dimercapto
Propane - 1- sulfonate)