Role of metal ions in biology and their toxic effects

PG Third Semester

Bioinorganic Chemistry-I

Lecture 1 & 2

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Contents

Books/References used and suggested

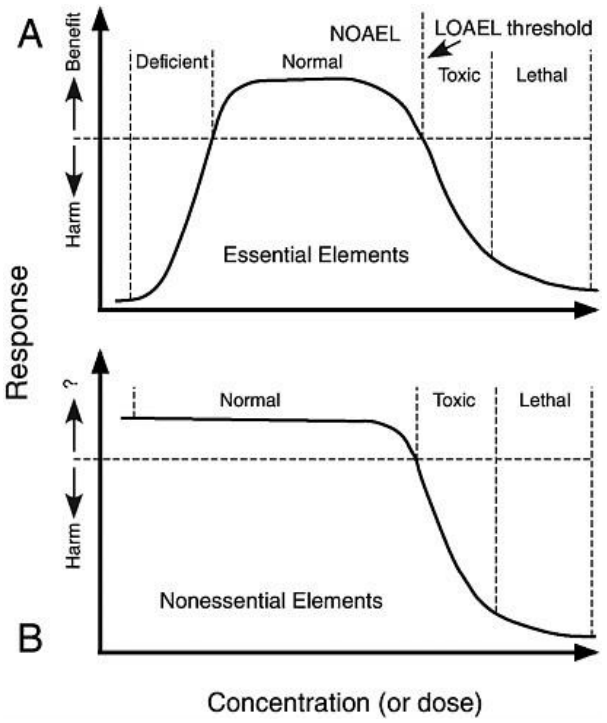
- Bioinorganic Chemistry by Bertini, Gray, Lippard and Valentine
- Inorganic Biochemistry by Cowan
- Bioinorganic Chemistry by A. K. Das
- Environmental Chemistry by A. K. De
- Oxford Chemistry Primer by Fenton

Essential elements in biology

- Essential metal ions are necessarily required in biological processes.
- About 40 essential elements are present in biology.
- Lighter elements (upto Z = 35) are biologically important (Exception: Mo, Sn, W, I)
- Classification is based on percentage or availability with respect to Human Body Weight.
- Three categories viz. bulk, trace and ultra trace.
- Amount of required metal ions does not measure the importance of the metal.

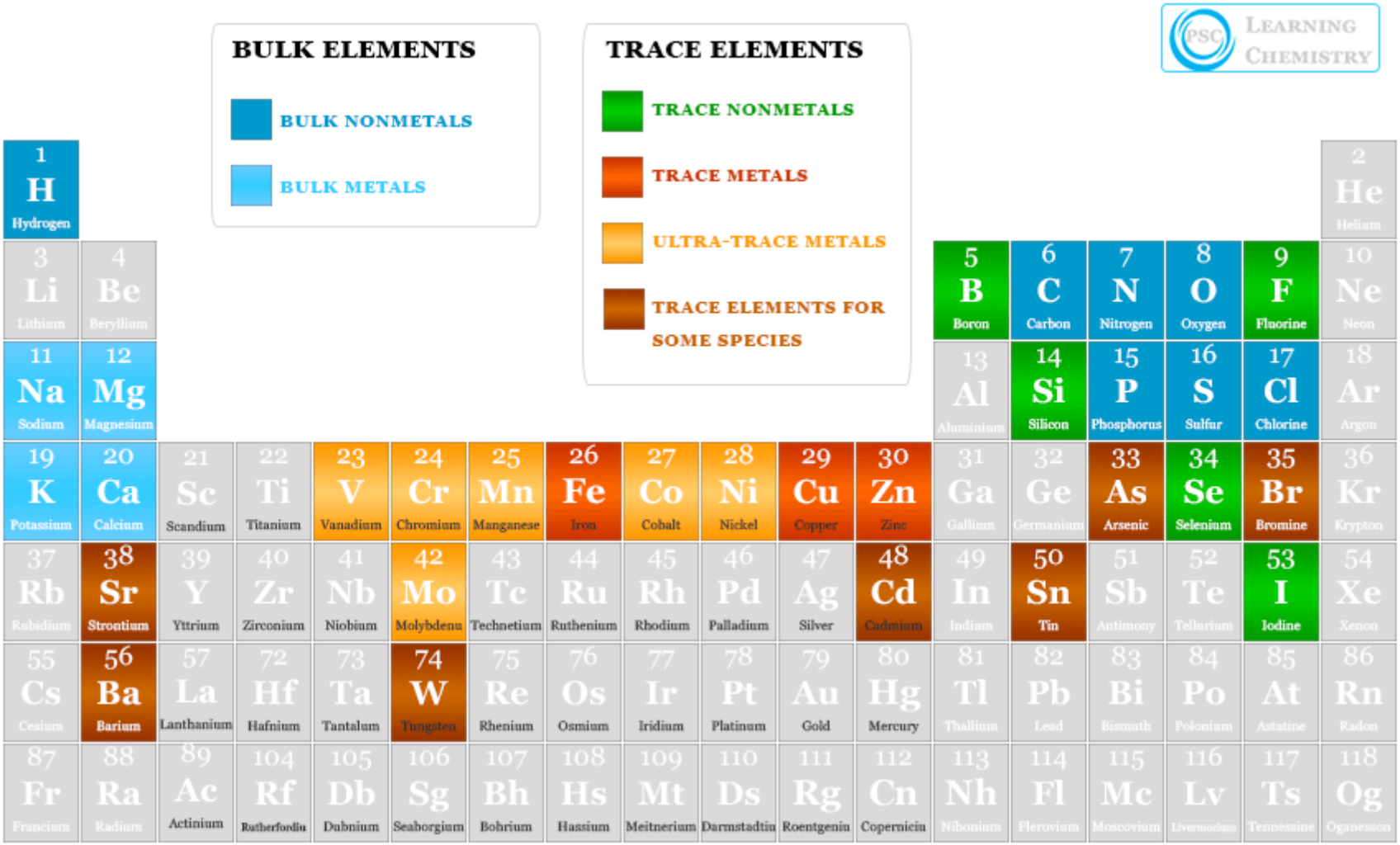
Bulk elements	Trace elements	Ultra trace elements
1-2% of HBW	< 0.01% of HBW Requirement 10^{-4}-10^{-1} $gmol^{-1}$	at ppm level, 0.0002% of HBW
H, C, N and O (constituent) Na, K, Ca, Mg, P, S, Cl	Fe (4-5 g), Cu, Zn Mn, Mo Co, F (2.6 g), I	Li, Si, V, Cr, Ni, Se, Br, Sn, W

- Biometals are classified as essential and beneficial metals
- Deficiency of essential metals lead to malfunctioning of biological processes (no survival)
- In absence of beneficial metals, life process gets hampered (not death)
- Role of metal ion can be structural (maintain structure) and functional (active site)
- Good correlation between bioavailability and geochemical distribution of metal ions exists.
- Pb, Cd, Hg are extremely toxic at trace amounts
- Essential elements can be toxic at higher concentration, lead to deficiency disease at lower concentration

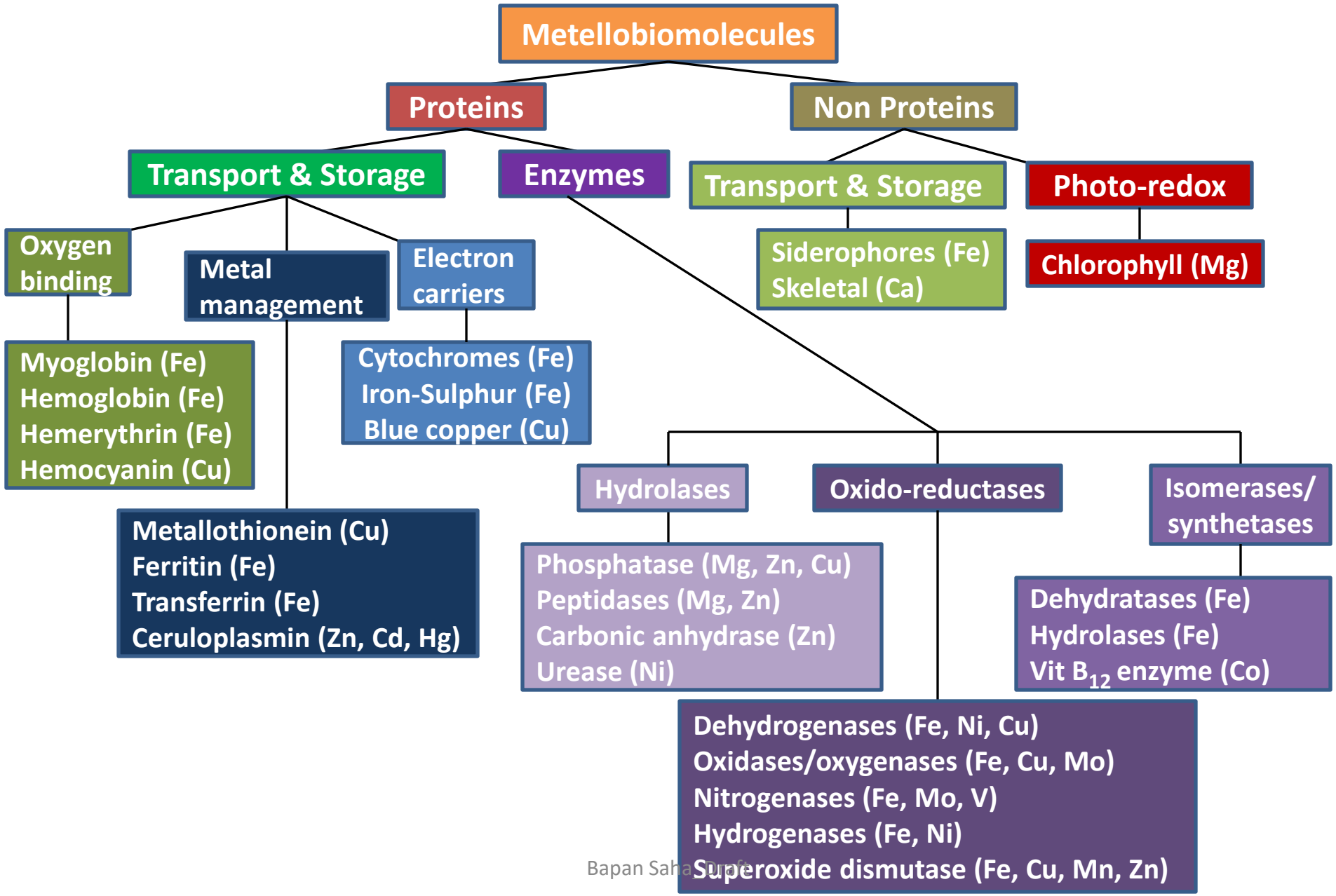


Variation of response of incoming dose

Essential and trace elements in biological systems



Metal ions in biological systems



Essential non metals

Elements	Biological function	Deficiency sign
F	Structure of teeth and bones, used as CaF_2 by some mollusks	Growth depression, dental caries
B	Control of membrane function, nucleic acid biosynthesis, lignin biosynthesis (weak evidences)	Growth of angiosperms, impaired nitrogen fixation
Si	Structural role in connective tissues and ontogenetic cell	Growth depression, bone and matrix deformities
P	Important constituents of DNA, RNA, bones, teeth, phospholipid, ATP, ADP and metabolic intermediates.	-
S	Essential in proteins (tertiary structure S-S links), involved in vitamins and fat metabolism.	-
Cl	Present in electrolyte and digestive juices.	Impaired growth in infants
I	Essential in many organisms, constituent of thyroid hormones-T_3 and T_4, important in metabolism and growth regulation	Goiter, reduced thyroid function
Se	Constituents of glutathione peroxidase, thioredoxin reductase enzymes, protection against oxidation of erythrocytes.	Muscle and pancreases degeneration, hemolysis

Essential metals

Elements	Biological function	Deficiency sign
Mn	Activates superoxide dismutase, carbohydrate metabolism, O_2-evolution reaction in photosynthesis	Growth depression, bone malformation
Mo	Used in enzymes with nitrogen fixation and nitrate reduction, Xanthine-oxidase	Growth depression
Co	Activates a number of enzymes (Vit-B_{12})	Pernicious anemia, growth retardation
Cr	Involved in glucose metabolism and diabetes, potentiates the effect of insulin.	Insulin resistance
V	Control of Sodium-pump, inhibition of ATP's, p-transferase	Reduced growth, impaired reproduction
Ni	Constituent of several enzymes like hydrogenases, plant ureases, CO dehydrogenases	Impaired liver function, reduced nitrogen utilization and iron metabolism.
Al	Activate succinic dehydrogenase and δ-aminolevulinate dehydrase (Heme synthesis)	-

Biochemical role of Na

- Sodium is a major cation of extracellular fluid (blood plasma and interstitial fluids).
- Actual concentration differs for different type of the cell, ($[Na^+]_{out}/[Na^+]_{in} = 15$)

Functions:

a) Important in nerve-functioning and transmission of signals

b) Regulates uptake of nutrients and flow of water across the cell membrane.

c) Involved in the transport of sugars and amino acids into the cells.

d) Maintains of osmotic pressure of the body fluid and regulates blood pressure

e) Helps in muscle contraction

Deficiency: Initially nausea, vomiting, loss of energy and confusion. Serious deficiency results hyponatremia causing seizures, coma even death

Treatment: Intravenous fluid of sodium solution

Excess: Elevated blood pressure (hypertension)

Biochemical role of K

- Potassium is a major cation of intracellular fluid.
- Actual concentration differs for different type of the cell, ($[K^+]_{out}/[K^+]_{in}=25$)

Functions:

a) Participates in glucose metabolism to produce ATP, protein biosynthesis and activation of enzymes such as pyruvate kinase.

b) Essential in transmission of nerve impulse and cardiac function

c) Balance body fluids and regulates blood pressure.

d) Helps in muscle contraction.

Deficiency: Fatigue, irregular heart beat, muscle weakness, increased urination, constipation

Treatment: at mild condition oral potassium pills and at severe condition potassium via intravenous mode

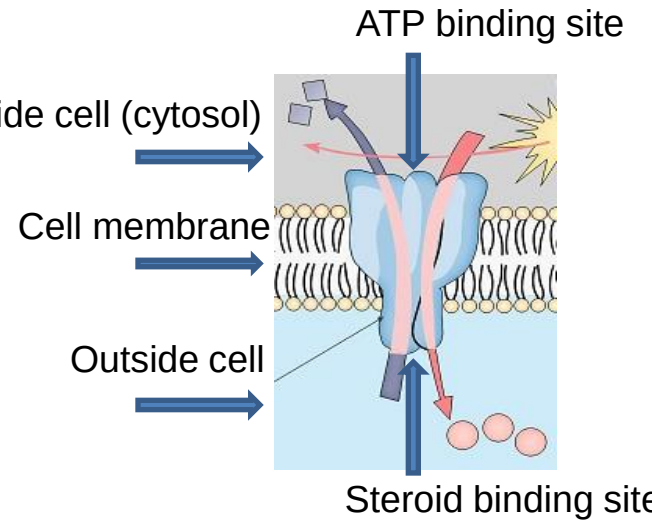
Sodium potassium pump (Na^+/K^+ ATPase)

- Ion pump maintains the active transport of ions across the cell membrane.
- The concentration gradient of Na^+ and K^+ ions across the cell-membrane is achieved by an energy repairing pump known as Na^+-K^+ pump (antiport).
- The pump transports three Na^+ out of the cell in exchange for two K^+.
- The pump is driven by an integral enzyme, Na^+/K^+ ATPase (P-type)
- The energy for required for pumping these ions is obtained from hydrolysis of intracellular ATP catalyzed by Mg^{2+}-ions.

$$3Na^+_{intra} + 2K^+_{extra} + Mg^{2+}\text{-}ATP^{4-} + H_2O \rightarrow 3Na^+_{extra} + 2K^+_{intra} + Mg^{2+}\text{-}ADP^{3-} + H_3PO_4^{2-} + H^+$$

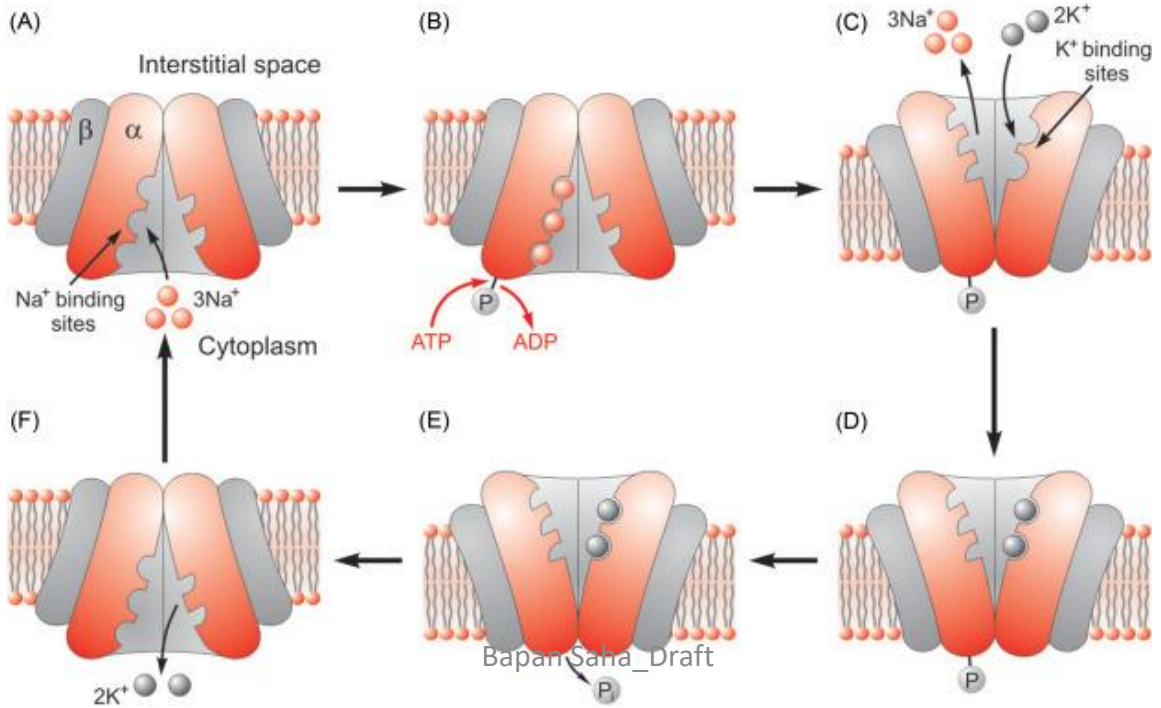
- Different Na^+/K^+ ratio (and the correct concentrations of Na^+ and K^+) inside and outside the cell develops an electrical potential across the membrane (essential for functioning of nerve & muscle cells).

- The Na^+/K^+ ATPase exists in two forms, depending on its orientation to the interior or exterior of the cell and its affinity for either Na^+ or K^+ ions.
- The enzyme Na^+/K^+ ATPase (280 kD) is a tetrameric ($\alpha_2\beta_2$) protein.
- The larger unit (two α units, 100 kD) contains the ATP binding site (acts as revolving door, pass through plasma membrane).
- The α-chains contain the selective metal binding sites and phosphorylation sites (one end).
- Other end of α chains has the steroid inhibitor binding site
- The α chains traverse the plasma membrane
- The smaller unit (two β units, 40 kD) primarily contains carbohydrate.



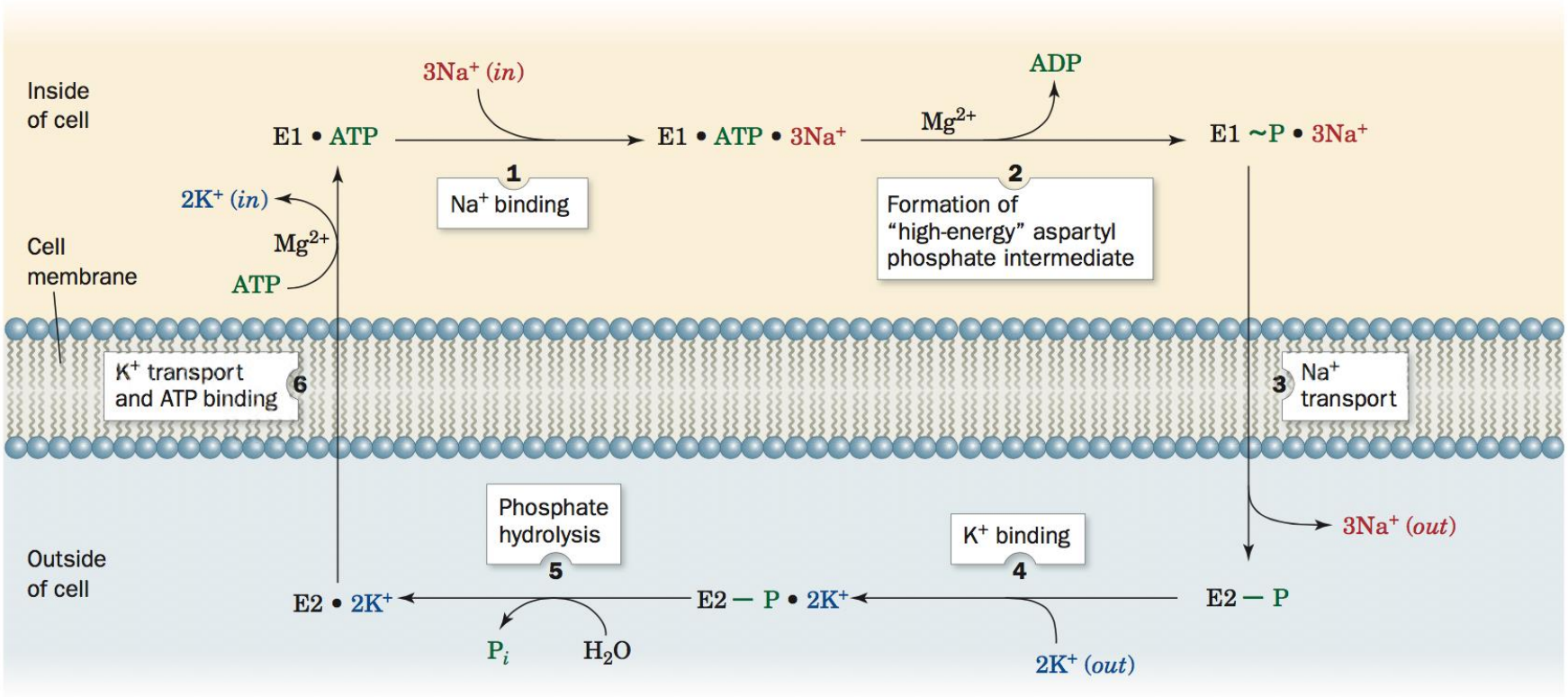
Mechanism of sodium potassium pump

- Na^+/K^+ ions are pumped against their concentration gradients by the enzyme Na^+/K^+ ATPase coupled with hydrolysis of ATP catalyzed by Mg^{2+}-ions.
- In the function of Na^+/K^+ pump, one cycle involves the transport of $3Na^+$ ions from inside the cell to the outside and $2K^+$ ions from outside the cell to inside the cell
- Binding of $3Na^+$ ions with the protein (α_2 unit) changes the local polarities to facilitate the binding of ATP, α_2 unit is phosphorylated and ADP is released after hydrolysis



- The phosphorylation changes the conformation (eversion) of protein (E1)
- In this conformation, the Na^+-binding sites become open and three Na^+ is released to the extracellular fluid
- The open channel binds two K^+ from outside causing dephosphorylation from the protein chain.
- Conformational changes (eversion) then again occur (E2), opening the K^+-binding site to cytosol finally leading to release of two K^+
- This leads to the original conformation of enzyme to initiate a new cycle again.
- The overall process of the uphill transport of Na^+ and K^+ ion is

$$3Na^+_{intra} + 2K^+_{extra} + Mg^{2+}\text{-}ATP^{4-} + H_2O \rightarrow 3Na^+_{extra} + 2K^+_{intra} + Mg^{2+}\text{-}ADP^{3-} + H_3PO_4^{2-} + H^+$$



- E1 projects the ion binding sites towards the cytosol, E2 projects the same outside the cell
- Na^+ binding triggers phosphorylation (E1) and K^+ binding triggers dephosphorylation (E2)

Role of Mg^{2+} ion:

- Mg^{2+} plays two crucial roles viz. Catalyzes the ATP hydrolysis and structure forming effect to change the protein conformation.

Biochemical role of Ca

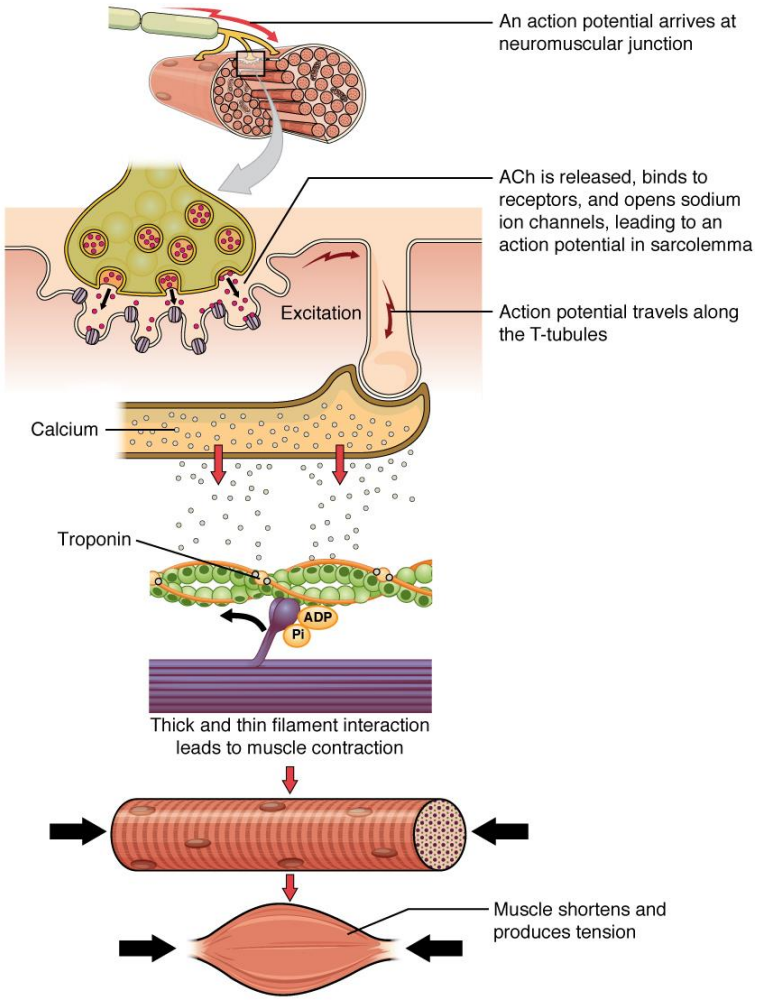
- Ca^{2+} ions (extra cellular fluid) is a major component of bones and shell (teeth)
- Bones - hydroxy apatite, $[Ca_5(PO_4)_3.OH]$ and Teeth - fluorapatite, $3[Ca_3(PO_4)_2]CaF_2$.
- It activates proteins and enzymes, participates in muscle contraction, blood clotting, glycolysis (metabolic degradation of glucose), gluconeogenesis (metabolic degradation of glucose) and messenger system for hormonal action

Deficiency: Osteoporosis, hypercalcemia or tetanin (spontaneous motor-neurons transmission), disturbed cardiac function.

- Excessive Ca^{2+} ions into a cell may damage it or cause apoptosis by necrosis.
- Excess of Ca^{2+} ions also lead to stone formation, hardening of arteries and cataract in eyes.
- Ca^{2+} concentration in plasma is controlled by calcitriol, parathyroid and calcitonin hormones
- Calcitriol promotes the absorption of Ca from gastrointestinal tract
- Parathyroid hormones elevate the Ca level in plasma by decalcification and reabsorption
- Calcitonin arrests gastrointestinal absorption of calcium from food and reduces its loss.

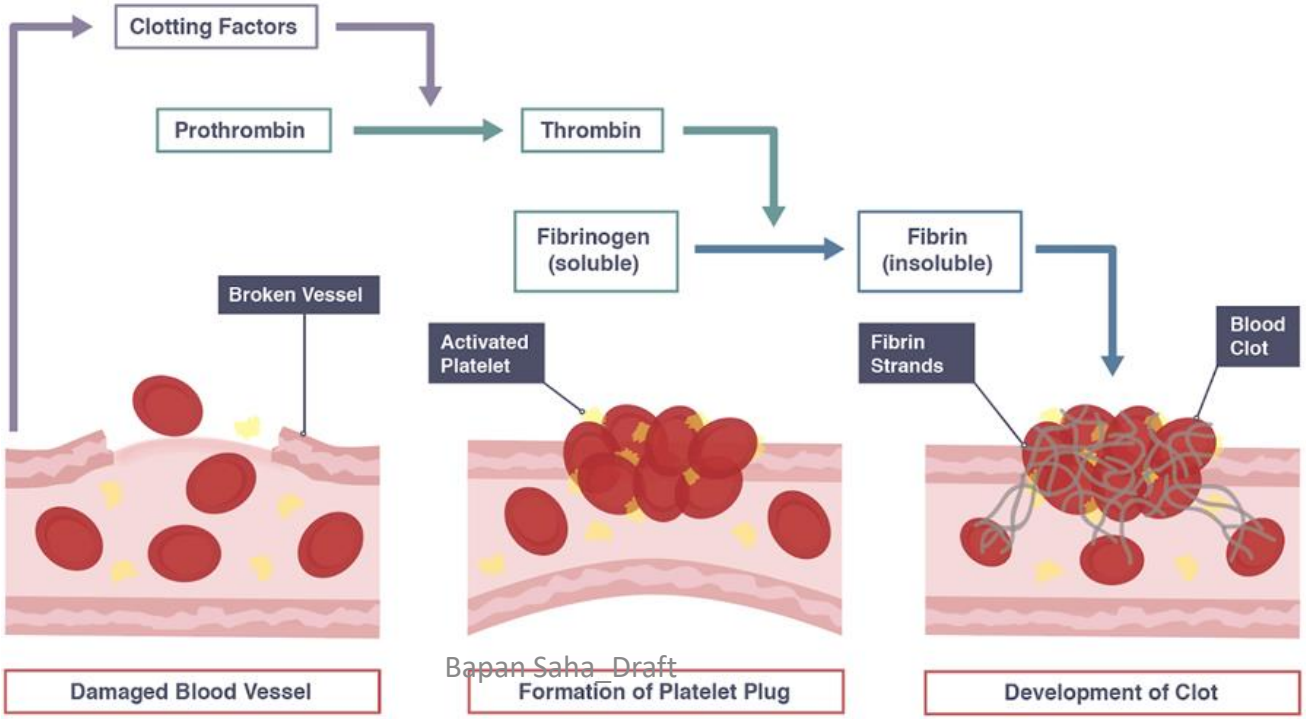
Muscle Contraction

- Ca(II) in the cytoplasm of muscle fibers (sarcoplasm) plays a regulatory role in muscle contraction
- Ca binds to troponin-C and calmodulin calcium modulated proteins, necessary for promoting muscle contraction.
- Release of Ca^{2+} ions from sarcoplasmic reticulum control the muscle contraction by allosteric mechanism
- Muscle contraction force arises from the joint interaction of actin, myosin and ATP
- Interaction between actin and myosin produces actomyosin.
- Actomyosin carries out hydrolysis of ATP and energy released from hydrolysis is used for muscle contraction



Blood clotting

- Blood clotting process involves several proteins with the participation of Ca^{2+} ions
- Formation of thrombin from prothrombin is of remarkable importance.
- Blood contains prothrombin, a soluble protein which is converted to the enzyme thrombin by the action of prothrombin activation in presence of Ca-ion.
- Thrombin, again aided by Ca-ion, clots the blood by converting its soluble fibrinogen into insoluble fibrin.



Biochemical role of Mg

- Mg is essential to all organisms, 25-30 g is present in human body.
- ~ 60% is present in skeleton and rest is primarily present in cell.
- The most important role is its involvement the photosynthetic activity chlorophyll.
- Mg(II) acts as a cofactor of several enzymes that catalyzes the hydrolysis of phosphates.
- Mg(II) is required in biological processes such as oxidative phosphorylation, DNA-transcription, RNA function, protein synthesis etc.
- It plays important role in stabilizing DNA and RNA structure through neutralization of negative charge present on phosphate backbone.
- Nerve impulse transmissions, muscle contraction and metabolism of carbohydrates are also associated to the interaction of Mg with nucleic acids.

Deficiency: Apatite, nausea, vomiting, weakness, fatigue, irregular heartbeat

Biochemical role of Fe

- Fe is the most abundant metal in biological system (4-5 g in human body), two oxidation states viz. Fe(II)/Fe(III) are interconvertible (0.77 to -0.50 V).
- About 75% of Fe is present in the erythrocytes of blood (Hb), 20% is stored as non heme iron (ferritin, hemosiderin, transferrin etc.) and 3-4% is present in myoglobin of muscle and rest in other heme protein (cytochromes, xanthene oxidase, peroxidase etc.).
- An adult human requires ~ 10mg of Fe-per day, for mensuration (~ 18mg) and pregnant or lactating women (~ 40mg) the amount is higher.
- High spin Fe(II)/Fe(III) complexes with bioligands are labile while that with low spin (porphyrin) are inert.
- Fe is used efficiently in oxygen transport and storage process in higher animals.

- It is involved in oxygen transport and in several other biochemical processes like DNA synthesis, energy production etc.
- Fe is not excreted during the course of metabolic function and hence its excessive intake can be harmful.

Fe-protein/enzyme	Function
Hemoglobin, myoglobin	Oxygen transport and storage
Cytochrome, Fe-S proteins	Respiration, electron transfer
Ferritin, hemosiderin	Fe storage
Transferrin	Fe transport
Metalloenzymes (oxidases, hydrogenases, reductases, nitrogenase, catalase, peroxidase)	oxygenation, H_2 production and consumption, nitrogen fixation, H_2O_2 metabolism

Deficiency: Anemia, β-thalassaemia, heart palpitations, irregular heartbeat

- Fe-deficiency is immediately reflected in terms of appearance of anemia
- Anemic condition may also arise from Vit B_{12} deficiency (pernicious anemia), erratic Cu metabolism, Pb poisoning and even sometime for genetic disorder (SCA)

Treatment: $FeSO_4$ pills coated with fructose or lactose, ferrous fumarate, ferrous gluconate etc. are clinically recommended. Sometime ascorbic acid is added with $FeSO_4$ to aid adsorption.

Toxicity: Hemochromatosis (bronze diabetes), hemosiderosis, lesions in gastrointestinal tract, liver damage.

Sickle cell anemia (SCA): Arises from the replacement of glutamic acid residue at 6-position in the β-chain with valine (hydrophobic side chain) in Hb

Biochemical role of Cu

- Cu is the third most abundant (200-300 mg in human body) metal in biology.
- Essential to all organisms and constituents of redox enzyme and hemocyanin.
- Also present in ceruloplasmin, cytochrome-c oxidase, catalase, superoxide dismutase (SOD).
- Dietary requirement of Cu is nearly 2-3 mg per day
- Absorbed in the intestines and carried to liver. Also found in heart, brain and even in kidney

Sources: organ meat, shellfish, fish, nuts and seeds as well as whole grains

Deficiency: demineralization of bones, anemia, decolorization of skin and hair, fragility of arteries, weight loss, muscle soreness, progressive brain disease in infants etc.

Treatment: Cu supplemented food, Cu(II)-(L-histidine) in Menkes' diseases

Excess: Wilson's disease (excess Cu in liver in brain due to its high intestinal absorption)

Treatment: Tetrathiomolybdate is used in treatment of Wilson disease.

Cu protein/enzymes	Metabolic functions
Ceruloplasmin	Oxidase activity and Cu transport, oxidation of Fe(II) and Fe-metabolism.
Cytochrome-c oxidase	Terminal oxidase enzyme in mitochondrial respiratory chain, involved in electron-transport.
Superoxide dismutase (SOD)	Intracellular and extracellular enzymes involved in defense against reactive oxygen species, destruction of superoxide radical
Tyrosinase	Enzymes catalyzing mechanism and other pigment production.
Blue copper protein and hemocyanin	Electron transfer and O_2 transport (molluscs/Arthropoda) respectively
Human serum albumin	Cu(II) transport

Biochemical role of Zn

- Zn is the second most abundant (2-3 g in human body) metal in biology
- Dietary requirement of Zn is about 10-15 mg per day.
- Zn is stored in kidneys and liver in metallothionine. The prostate gland is very rich in Zn.
- Essential constituent of enzymes (>70) such as carbonic anhydrase, carboxypeptidase, alcohol dehydrogenase, alkaline phosphatase, superoxide dismutase etc.
- Biochemical function of Zn is based on its Lewis acid character.
- Zn stabilizes coiled ribosomes and plays a significant role in sexual maturation (male) and reproduction (female-growth factor)

Sources: Coriander, prawn, garlic, mushroom, pea, nuts, fruit

Deficiency: Retarded growth, inhibition of sexual maturation, anemia, loss of appetite, test sensitivity, acne and rashes, poor neurological function etc.

Treatment: Zn-supplemented food and $ZnSO_4$ capsule is clinically recommended

Zn protein/enzyme	Functions
Carbonic anhydrase (known first, 1939)	Hydration of CO_2 and dehydration of H_2CO_3 (conversion of CO_2 to H_2CO_3 and vice versa)
Carboxypeptidase A (known second, 1955)	Hydrolysis of C-terminal peptide linkages during digestion of protein
Zn-finger protein	Recognize DNA base sequences during replication and transcription of DNA
Alcohol dehydrogenase	Catalyses the hydride transfer from alcohol to NAD^+
DNA polymerase	Polymerization of DNA with the formation of phosphate ester
Superoxide dismutase	Controls and stabilizes the enzyme SOD

Biochemical effects of Mn

- Its deficiency induces retarded growth, skeletal abnormalities, transient dermatitis, hypocholesterolemia, ataxia in infants, reproductive failure
- In glycoprotein synthesis, the Mn-dependent enzymes like glycosyl transferase, glactosyl transferase play important role. the impaired glycoprotein synthesis leads to skeletal abnormalities and ataxia.
- In glucose metabolism, Mn^{2+} actively participates in smooth functioning of pyruvate kinase.

Source: Whole grains, mussels, nuts, soybeans, leafy vegetables, black peeper, legumes, brown rice etc.

Treatment: Mn enriched food and sometimes $MnSO_4$ is clinically recommended.

Biochemical effects of Cr

- Cr is part of GTF (glucose tolerance factor) which includes one Cr^{3+} and provides aid in insulin binding to the site of action
- It helps in lowering the cholesterol and triglyceride levels
- Excess of Cr can be carcinogenic, causes skin and lung cancer

Biochemical effects of Co

- It is the metal center in Vit B_{12} (Cobalamin)
- It promotes RBC formation and activates some enzymes
- Excess of Co can result in vomiting and nausea, heart problems, thyroid damage
- Co deficiency may cause anemia

Some metal dependent Human systems

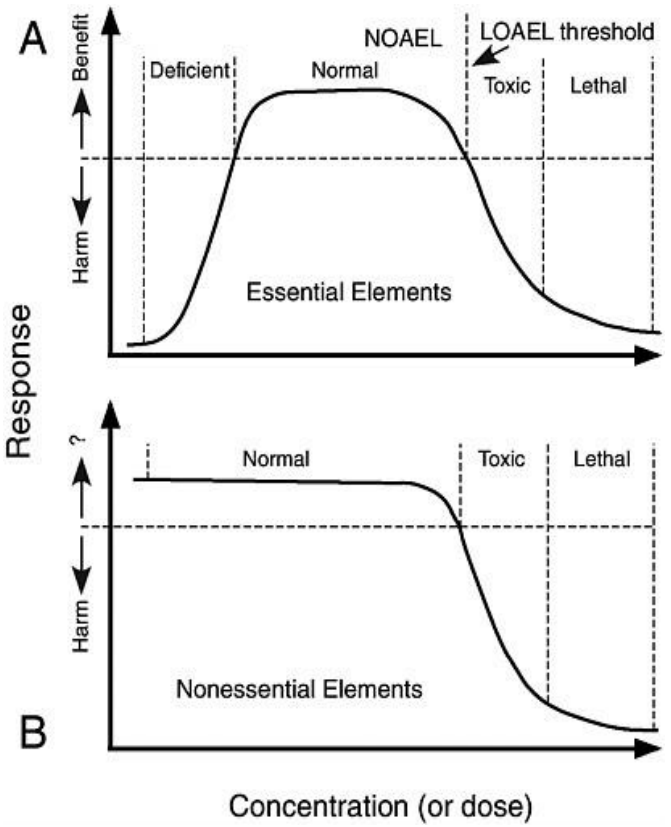
Human systems	Metal disbalance	Diseases
Nerve	Na, K, Mg, Ca	Epilepsy, personality change
Muscular	Na, K, Fe	Myotonia
Cardiovascular, Heart, Blood	Mg, Ca, Na	Hypertension
Blood Vessels	Na, K, Fe, Cu	Heart failure
Digestive, Liver	Zn, Fe Cu	Liver cirrhosis Wilson disease
Urinary	K, Mg, Ca	Renal insufficiency
Bone and skeleton	Ca, Mg	Osteoporosis

Chemical Toxicology

- Chemical toxicology is the study of toxic chemicals and their modes of action.
- Toxicity is the degree to which a chemical can damage an organism.
- Toxic chemicals disturbs the biochemical processes.
- Metals listed as environmental hazards (Al, Co, Pb, Hg, Mo, Ag, Sn, Zn etc.) can be essential in trace amount.
- Defining the essential and toxic limit of an element is confusing.
- Schwartz coined the term “concentration window” to draw arbitrary lines of demarcation.

  Essential at trace levels for sustaining life, deficient at lower level than essential limit and toxic at higher level than essential limit.

- Toxicity can occur by the pathway of administration (applied on skin, ingested, inhaled, injected), the time of exposure (short/long term), the number of exposures (a single/multiple doses over time), the physical form of the toxin (solid, liquid, gas), the genetic makeup of an individual.
- Toxic metals can sometime imitate the action of an essential element and thereby interfering with the metabolic process.
- Metals in one oxidation state may be essential (Cr(III)) while in other it can be toxic Cr(VI-carcinogenic)



Variation of response of incoming dose

- Toxic chemicals can be classified according to their function and effect exerted on the body (mutagens, carcinogens etc.)
- Toxic chemicals can attack at the active site of enzymes/metalloenzymes inhibiting their function/action
- For example, Hg(II)/As(III) ions can attack at S-atoms present in the active sites of enzymes and Cd(II) can substitute Zn(II) in metalloenzyme, resulting in toxicity.

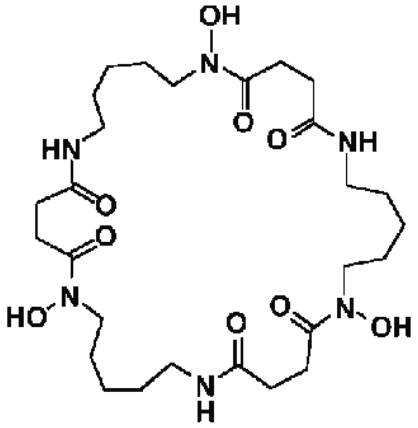
General aspect of mechanism of toxicity

- Replacement of certain active moiety (phosphate by arsenate)
- Deposition of excess metals in vital organs (severe irritations)
- Cell damage by radiation from the radioactive elements (malignancy or mutation)
- Interference through competitive inhibition (Se may replace S in amino acids)
- Interference with the proteins and enzymatic process (heavy metals affinity for -SH group).

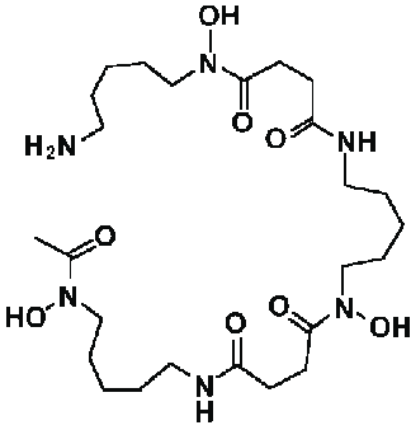
Toxicity of Iron

- Fe is essential to all organisms and is not excreted
- Excessive intake for long duration may lead to Fe-deposition and Fe-toxicity.
- The excess of Fe is deposited primarily in liver, heart and kidney.
- Acute Fe toxicity results from an accidental intake of Fe(II) tablets causing erosion of the gastrointestinal tract.
- Fe overload leading to chronic Fe poisoning arises in some genetically disordered diseases.
- Chronic Fe poisoning may also arise from regular excess intake of iron from cooking vessels. For example, African siderosis (hemosiderosis) found in the members of Bantu tribe in South Africa, who consume beer brewed in iron pots.
- In hemosiderosis, Fe is deposited in different parts of the body among the patients receiving repeated blood transfusions.

- In hemochromatosis (a genetic disorder), deposition of Fe occurs in organs like liver, spleen, pancreas and skin. It may result in liver cirrhosis, pancreatic fibrosis and bronze pigmentation on the skin (bronze diabetes).
- Fe poisoning is a leading cause deaths in children (prenatal/paediatric).
- The chelating antidote used for detoxification of Fe is the siderophore desferrioxamine, having a very high thermodynamic affinity specially for Fe(III).



desferrioxamine E



desferrioxamine B

Toxicity of Aluminium

- Al is toxic to most plants and slightly toxic to mammals.
- Commercial deodorant, baking powder also contain Al. Moreover, Al foil and Al cookware that we use also chief source of Al deposition in body.
- Al(III) is a hard cation and has tendency to bind strongly to N- and O-donor ligands in biomolecule and deactivate them.
- Alzheimer's disease arises from increased Al(III) concentration in brain tissues. Al(III) crosses the blood brain barrier and is progressively deposited in large pyramidal neurons of the hippocampus, cortex and other regions vulnerable in Alzheimer's disease.
- It is called the soft in head mineral because it is associated with memory loss and dementias
- Once absorbed, Al accumulates in bone (majority), brain, liver and kidney leading to osteoporosis

- Al(III) can inhibit δ-aminolaevulinic acid dehydratase (ALAD) involved in biosynthesis of heme. ALAD binds eight Zn(II) ions for its enzymatic activity. It probably competes with Zn(II), inhibits the enzyme resulting in anaemia.
- Al(III) can also inhibit different Mg-dependent enzymes like kinases and ATPase.
- Al-toxicity are also associated with renal function, and breast and prostate cancer
- Tea plants accumulate Al(III) and stores it in leaves. On addition of milk, insoluble $AlPO_4$ is formed and reducing its bioavailability. But in lemon tea, formation of soluble Al(III)-citrate complex facilitates the absorption of Al(III) in gastrointestinal tract.
- Presence of $Al(OH)_3$ and $Si(OH)_4$ in Al(III)-based antacids results the formation of hydroxyaluminosilicates (stable in intestine), thereby reducing bioavailability of Al(III).
- 1,2-dimethyl-3-hydroxypyrid-4-one (L1) and desferrioxamine are recommended for Al detoxification.

Toxicity of Copper

- Cu is essential for all forms of life.
- Cu is primarily absorbed in brain and organs like liver, kidney and intestine.
- Problem arises when it is in excess. To be toxic, Cu intake must be in gram amounts or continual intake of ~ 250 mg/day.
- Excess Cu leads to irritation of gastro-intestinal tract.
- Wilson's disease arises due to genetic disorder in Cu-metabolism. Cu-metabolism is prohibited due to interference in synthesis of ceruloplasmin or any impairment of Cu-binding to this protein.
- In Wilson's disease, large amount of copper is present in blood stream, damaging the erythrocyte membrane. Cu is finally deposited in liver and brain developing the hepatic and neurologic disorders respectively.

- Symptom of Wilson's disease are hepatic cirrhosis (liver damage), neurological damage, brown/green rings in the cornea of the eyes, lack of coordination (ataxia), progressive mental deterioration.
- Some other features Wilson's disease are: low levels of Cu in plasma and increased excretion in urine, high intestinal absorption of Cu, renal damage due to deposition of Cu leading to an increased excretion of amino acids, proteins, hemoglobin through urine.
- To reduce the Cu-overload, the chelating drugs like $Na_2Ca(EDTA)$, 2,3- dimercaptopropan-1-ol (BAL), D-penicillamine are clinically recommended.
- Zn-salts are also recommended for the treatment of Wilson's disease.
- Trien(triethylenetetramine) can also be used to allow the excretion of copper through urine.
- Tetrathiomolybdate prevents the absorption of Cu by forming insoluble Copper thiomolybdate in the gut and can also be used in treatment of Wilson's disease.

Calcium toxicity

- Ca-salts are not soluble and precipitated resulting in formation of stones in kidney, gall bladder and cataract in eyes.
- Stone formation may also lead to hardening of arteries.

Radionuclide toxicity

- Radionuclides (even trace amount) show toxicity because of their ionizing radiation which can damage the living tissues. Nuclear radiation can interact with biomolecules too.
- Radionuclide like 239Pu emits α-particles which induces malignancy in bone, liver, lung and lymph nodes.
- 90Sr is known to produce bone cancer.
- 137Cs can follow the biochemical pathway of potassium and distributed throughout the soft tissue and it irradiates to cause cancer.
- Organs affected: 42K (muscle), 60Co (liver), 35S (skin), 85Kr (ovaries), 131I (thyroid), 90Sr (bone), 222Rn (lungs), 226Ra (bones), 137Cs (whole body).

Manganese toxicity

- Arises due to inhalation of Mn-ores through dust.
- May lead to hepatolenticular degeneration resembling Parkinson's disease.

Nickel toxicity

- Can produce bronchial cancer
- It causes dermatitis and interferes with the activities of the enzymes like isocitrate dehydrogenase, cytochrome c oxidase etc.

Vanadium toxicity

- Inhibits the synthesis of amino acids, phospholipids and cholesterol.
- Inhibits the activities of enzymes like tyrosinase, nitrate reductase.
- Vanadate which is similar to phosphate can inhibit Na+-K+ ATP-ase.

Cobalt toxicity

- Heart failure (excessive consumption of beer)
- Affects the Hb content and sometime can produce polycythaemia.

Zinc toxicity

- Zn dust ingestion causes respiratory problems known as zinc fume fever.
- Chronic Zn poisoning can also cause anorexia, paralysis, diarrhoea, dyspepsia etc.

Chromium toxicity

- Cr(VI) can transport in cell as CrO_4^{2-}.
- On reduction by –SH group (glutathione) produces Cr(V) and Cr(IV) intermediates which interact with DNA to induce carcinogenicity.

Molybdenum toxicity

- Impaired growth, diarrhoea, skin disease, loss of hair.
- Diminishes intestinal absorption of copper.

Metals as carcinogen

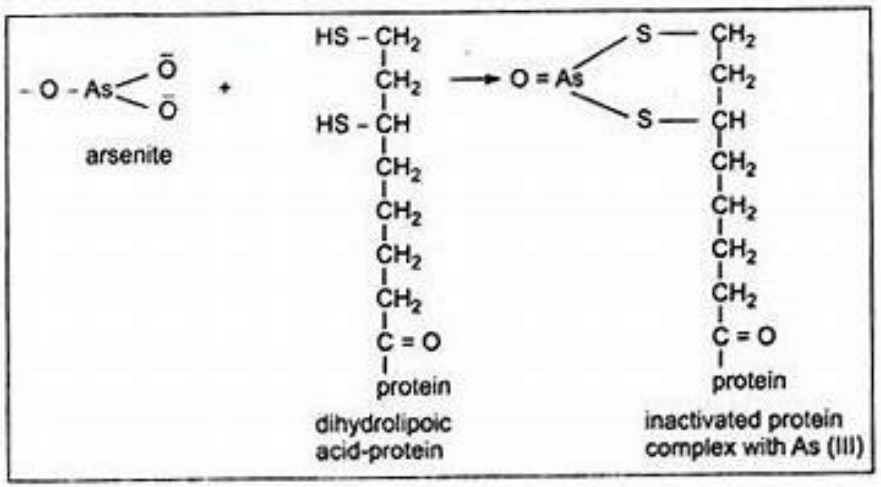
- Ni, Cr and Cd are the three most effective carcinogenic metals.

Toxicity of Arsenic(III)

- Excessive withdrawal of ground water is the main cause of As-contamination in water.
- As - content in drinking water ranges from 0.05-3.5 mg/L & permissible limit is 0.05 mg/L
- Arsenic compounds are mostly found in insecticides, fungicides and herbicides.
- It has been used as a therapeutic agent and as a poison (perhaps Napoleon was poisoned)
- Arsenic exposure is usually suicidal, homicidal or occupational
- As(III) is the most toxic and is a carcinogen (lung and skin cancer)
- Three major biochemical actions of As(III) are coagulation of protein, complexation with coenzymes and uncoupling of phosphorylation.
- The toxicity due to As-compounds arises from three possible routes
- Mechanism: Inhibition of –SH (sulfhydryl) in cellular enzymes and replacement of phosphate molecules in “high energy” compounds

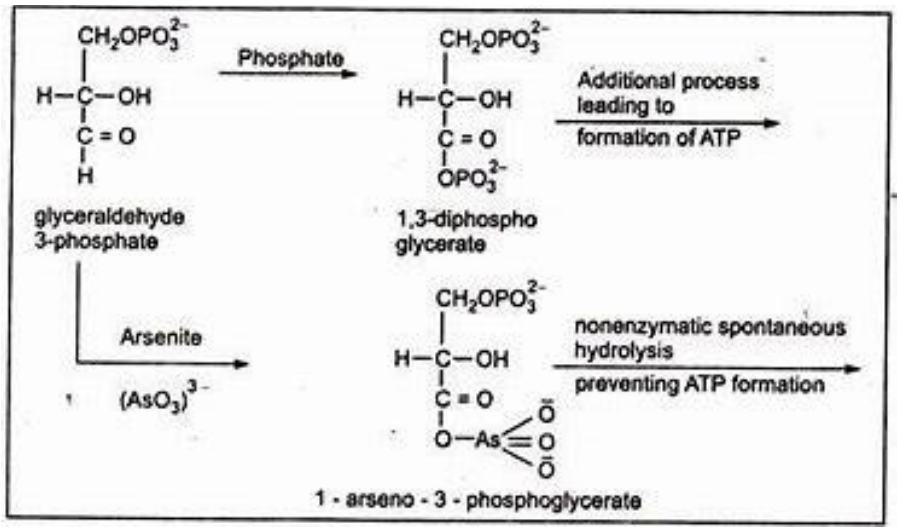
Blocking of -SH group in enzymes

- As(III) being soft binds with -SH group containing enzymes, thereby inhibiting the enzyme action. The enzymes which generates cellular energy in citric acid cycle are adversely affected. The inhibitory action is based on activation of pyruvate dehydrogenase by complexation with As(III) thereby preventing the generation of ATP.
- As(III) can also inhibit the enzyme which is involved in DNA repair mechanism i.e., poly(ADP-ribose)polymerase. It is also responsible for inducing heavy atom effect by binding methyl transferase



Competitive inhibition of different enzymes

- As(III) interferes with biochemical processes involving P such as enzymatic synthesis of 1,3-diphosphglycerate from glyceraldehyde-3-phosphate through oxidative phosphorylation thereby producing 1-arseno-3-phosphoglycerate which hydrolyses without generating ATP (AsO_3^{3-} vs PO_4^{3-})
- As-compounds can inhibit phosphoenolpyruvate mutase required for the biosynthesis of C-P bonds in living bodies

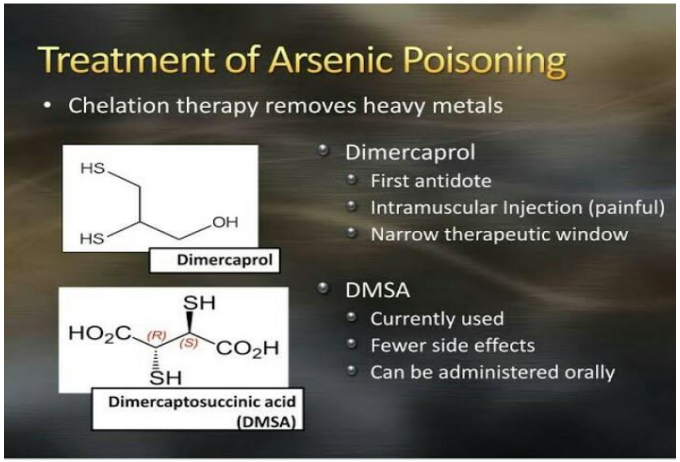


Denaturation of proteins

- Excess of As(III) can denature (coagulate) proteins by attacking the -SH groups required in maintaining the its secondary and tertiary structures.

Clinical symptoms of Arsenic poisoning

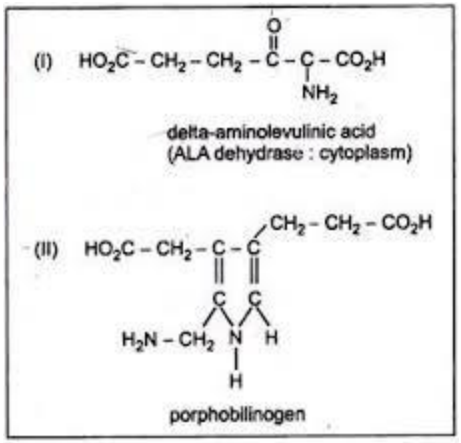
- Initial stage: gastroenteritis, dermatitis, keratosis.
- Second stage: depigmentation and hyperkeratosis, peripheral neuropathies, melanosis.
- Last stage: Gangrene of feet (Blackfoot disease), ulceration in the limbs and skin cancer.
- Urine sample provide the most reliable diagnostic testing
- Antidote should be capable of binding As(III).
- Should have -SH group
- BAL or dimercaprol was first used
- DMSA is currently in use

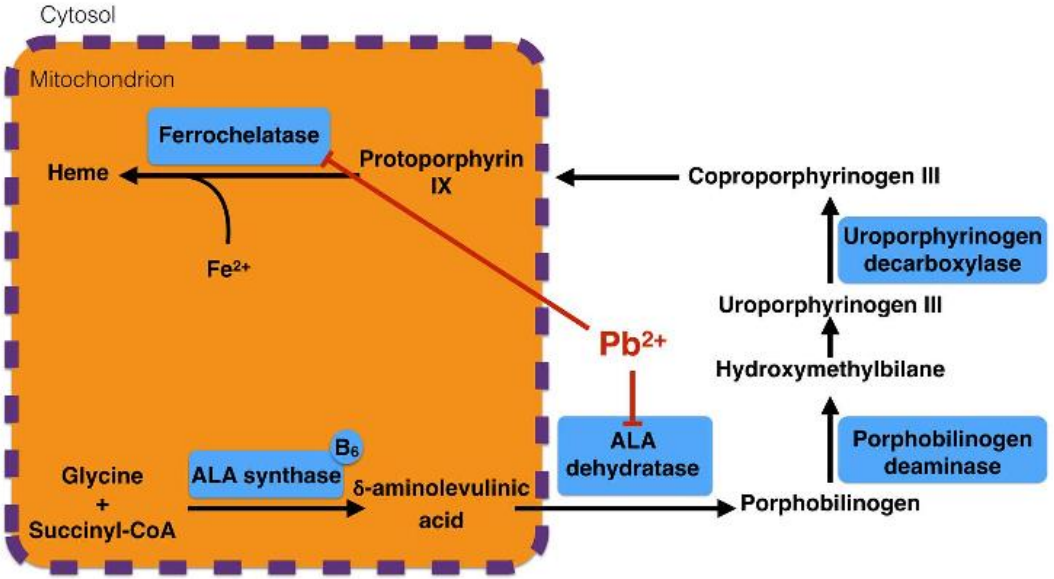


Toxicity of Lead

- Pb is the most abundant heavy metal, occurs as Pb minerals.
- Major source of air borne Pb is the combustion of leaded petrol or gasoline along with paints, batteries etc.
- Pb intake is mostly from diet (200-300 µg/day), air and water contribute ~ 10-15 µg/day.
- 200 µg/day of Pb is excreted while almost 25 µg/day is stored in bones.
- Almost 70-90% of Pb is accumulated in bones followed by liver and kidney.
- Pb(II) readily replaces Ca(II) in bones, either firmly fixed or reversibly fixed.
- On reversible binding, Pb may get released in blood stream from bone tissue.
- At the initial stage, Pb is stored in bones and when the body requires essential elements like Ca/P, blood starts leaching out these elements from bone and thereby exerting toxic action of Pb.

- Major biochemical effect of Pb is its interference with heme (porphyrin) synthesis. It interacts with the enzyme δ-aminolevulinate dehydrase to inhibit the formation of porphobilinogen which acts as the building block unit for the biosynthesis of porphyrin skeleton. Pb(II) probably competes with Zn(II) center required for the activity.



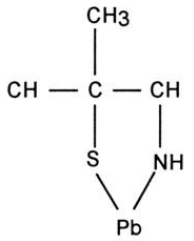


- Pb poisoning (Pb-content in blood > 0.8 ppm) in severe cases leads to anemia, damages nervous system by irreversible brain damage.

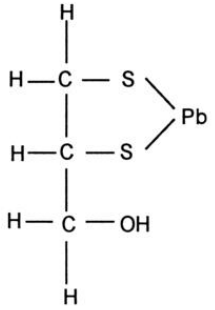
- Pb can damage the mitochondria of kidney allowing the loss of glucose, amino acids and phosphate through urine. It can also damage the liver and gastrointestinal track.
- Pb poisoning also cause enzyme inhibition, cellular dysfunction, chronic nephritis, neurological problems, and even exerts reproductive and teratogenic effects.
- Pb poisoning is common in children (developing brain) due to their propensity of chewing objects containing the Pb based paints having sweet taste

System	Symptoms
General	Anaemia
Digestive	Constipation, loss of appetite, pain in abdomen
Muscular	Loss of coordination and strength, tiring
Nervous	Peripheral motor paralysis, insomnia, dizziness
Vascular	Diminished hemoglobin, arteriosclerosis, hypertensin
Other organ	Lead line in gums, lower sperm count, miscarriages, loss of vision, join pain

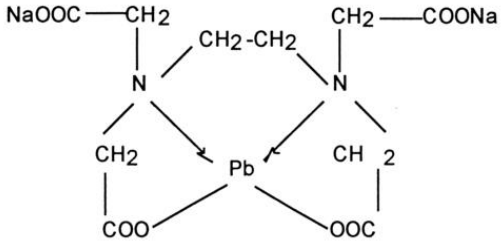
- Pb poisoning can be cured by treatment with chelating agents that binds Pb effectively.
- Ca-chelating agent like $CaNa_2EDTA$ in solution is fed to the patient with Pb poisoning, Pb displaces Ca from the chelate and excreted via urine.
- Typical chelating agents used are EDTA, BAL, D-penicillamine and succimer.



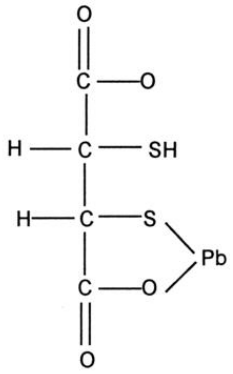
Pb- PENICILLAMINE



Pb - BAL



Pb - $CaNa_2EDTA$



Pb - SUCCIMER

Toxicity of Mercury

- Hg is the most toxic heavy metal with natural abundance in soil is ~ 0.1 ppm
- Minamata Disease in Japan (1953), the effluent from a vinyl chloride plant was the main source of Hg.
- Hg-poisoning from wheat in Iraq (1972) and in US (1996).
- Hg compound is used as pesticides and fungicides (results its distribution in environment). It is also widely used as electrodes and in different electrical apparatus
- Mercury contamination of tuna - currently a problem
- The inorganic Hg-compounds are very often absorbed on sediments and may be biomethylated subsequently.
- Hg toxicity or poisoning is a disease caused by exposure to Hg or its compounds. The toxicity of Hg depends on its chemical form.
- Elemental Hg is fairly inert and non-toxic. If swallowed, it is excreted without serious damage.

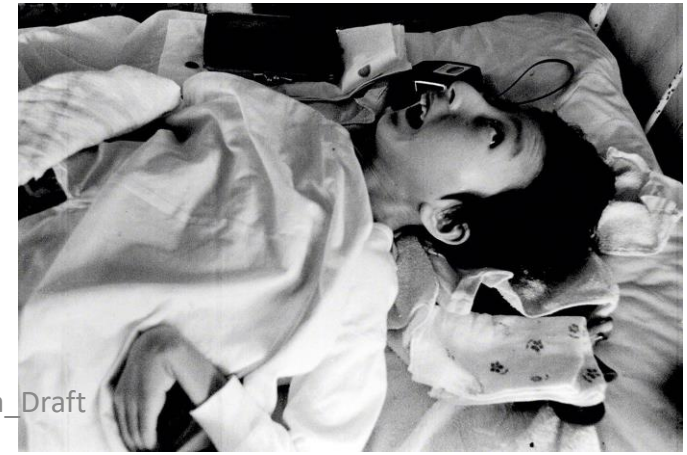
- Hg vapor when inhaled (due to its low vapor pressure), enters the brain through the blood stream, leading to severe damage of the central nervous system.
- Hg_2^{2+} ion forms insoluble salts chloride ions. Our stomach contains a fairly high concentration of chloride and hence Hg_2^{2+} ion is not toxic.
- Hg^{2+} ion is fairly toxic. Because of its high affinity for S-atoms, it is easily attached to the S-containing amino acids of proteins. It also forms bonds with hemoglobin and serum albumin, both of which contain sulphydryl groups. Hg^{2+} ion does not travel across biological membranes and hence does not get access into biological cells.
- Organomercurials (CH_3Hg^+ at 0.5 ppm) is the most toxic of all. RHg^+ is soluble in fat, lipid fraction of membrane and the brain tissue and therefore retained in cell for prolonged period. The most dangerous aspect is its ability to move through the placental barrier and enter foetal tissues (teratogenic effect).

- CH_3Hg^+ may inhibit the normal functioning of the brain (neurological disorder).
- Attachment of Hg to cell membrane is likely to inhibit active transport of sugar across the membrane and allow the passage of K^+ to the membrane. In brain cell this would result energy deficiency and disorder in the transmission of nerve impulses.
- Babies born to mother subjected to CH_3Hg^+ poisoning suffer from irreversible damage to central nervous system such as mental retardation etc.
- CH_3Hg^+ poisoning also leads to segregation of chromosome (chromosome breakage and inhibition of cell division)

Species	Biochemical impact
Hg	Non toxic, vapour is highly toxic when inhaled
Hg_2^{2+}	Insoluble as chloride, low toxicity
Hg^{2+}	Toxic, not easily transported across biological membrane
CH_3Hg^+	Highly toxic, causes irreversible nerve and brain damage, easily transported to biological membrane and stored in fat tissue.
$(CH_3)_2Hg$	Low toxicity, can be toxic on its conversion to CH_3Hg^+ in acidic medium

Tragedy of Minamata

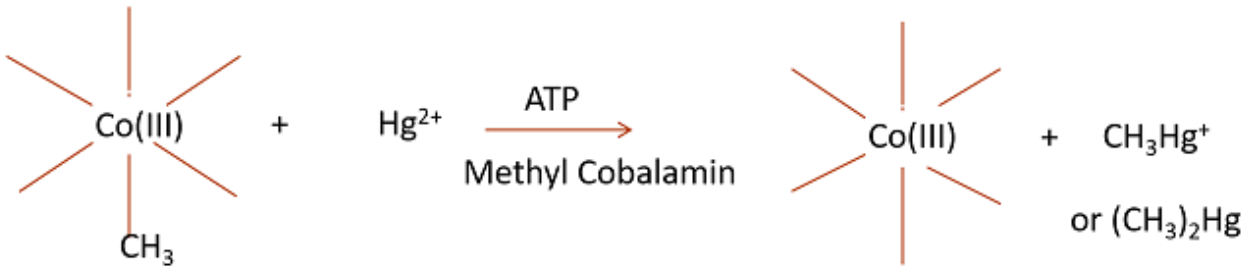
- Minamata disease is a neurological disease caused by severe Hg-poisoning. Signs and symptoms include numbness in the hands and feet, general muscle weakness, loss of peripheral vision, and damage to hearing and speech. In extreme cases insanity, paralysis, coma and death follow within weeks of the onset of symptoms.
- Minamata disease (Minamata city, Japan in 1956) was caused by the release of CH_3Hg^+ in the industrial wastewater from the chemical factory (Chisso Corporation). This highly toxic chemical bioaccumulated and biomagnified (CH_3Hg^+) in fish and shellfish in Minamata Bay, which when eaten by the local population, resulted in mercury poisoning.



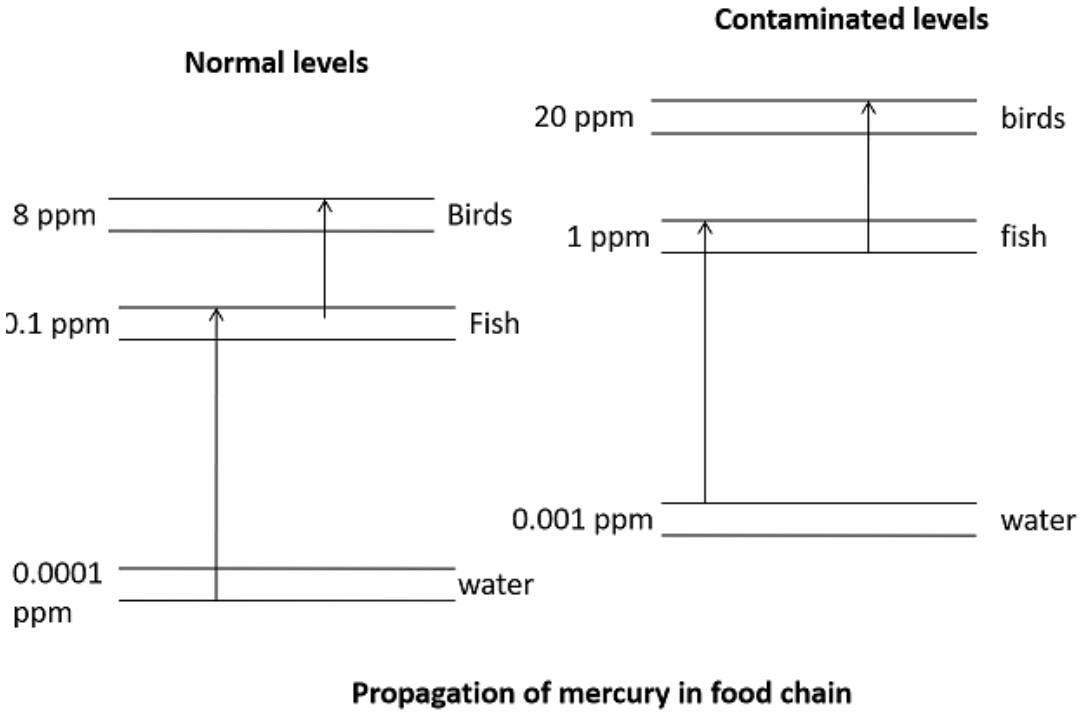
- All forms of Hg are toxic to the fetus, but methylmercury most readily passes through the placenta and maternal exposure can lead to spontaneous abortion or other issues.
- Clinically see: visual disturbances, ataxia, hearing loss, mental deterioration, muscles tremors, paralysis and even death.
- For detoxification of Hg(II) or CH_3Hg^+, D-penicillamine (DPA-$C_5H_{11}NO_2S$), N-acetyl-D-penicillamine derivative (NAPA-$C_7H_{13}NO_3S$) and unithiol (2,3-dimercapto-1-propansulfonic acid) are recommended.
- In detoxification of CH_3Hg^+, NAPA is a better antidote than DPA because of the presence of the lipophilic acetyl group in NAPA.
- Natural Chelators: A detoxification mechanism has been traced in some Hg-resistant bacteria. Chlorella (from algae) is a natural immune stimulant and has a high affinity for heavy metals (it contains sulfur bound amino acids and acts as a natural chelator)
- However, the reduction of use of Hg(II) products like Hg-electrodes, Hg-based pesticides, Hg-based electrical appliances are desired for environmental remedial.

Biological methylation: Amplification in food chain

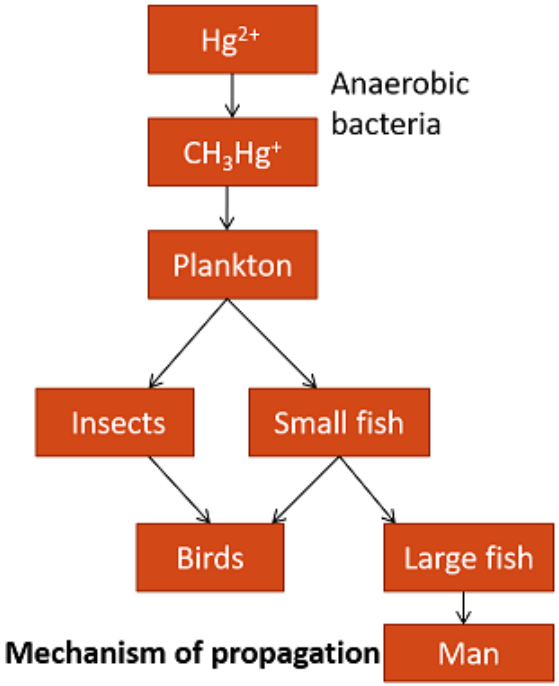
- Hg or its salts can be converted into methyl mercury by anaerobic methane synthesizing bacteria in water (Biological methylation process). This conversion is facilitated by Co(III)-containing vitamin B_{12} coenzyme. A CH_3-group bonded to Co(III) on the coenzyme is transferred enzymatically by methyl cobalamin to Hg^{2+}, yielding CH_3Hg^+ or $(CH_3)_2Hg$.
- Acidic medium promotes the conversion of $(CH_3)_2Hg$ to CH_3Hg^+ which is soluble in water and it enters the food chain through plankton and further concentrated by fish by a factor 1000 or more as passes through food chain.



Propagation of Hg in food chain



Propagation of mercury in food chain

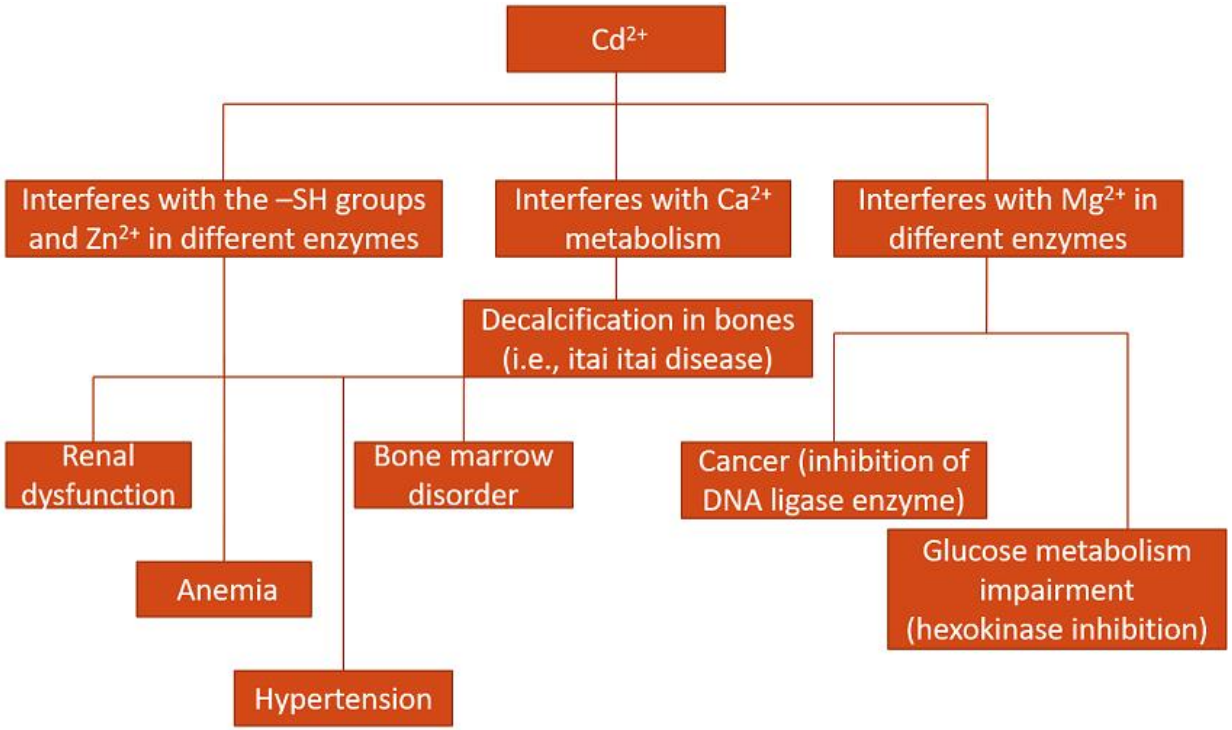


Mechanism of propagation

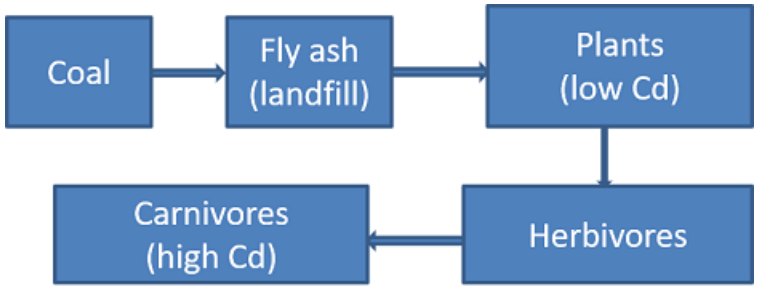
Toxicity of Cadmium

- Cd occurs in nature in association with Zn minerals.
- Surce: Pigments (CdS, CdSe), Ni-Cd battery, nuclear reactors (used to slow down the neutron flux), semiconductors, electroplating industries, welding electrodes, etc.
- Majority ingested Cd is trapped on the kidneys and mostly got eliminated.
- A small fraction is bound effectively by metallothionine (-SH sites) in kidney, leading to its disfunction and the remaining is stored in body and gradually accumulate with age.
- Ca^{2+} deficient diet enhances Cd^{2+} accumulation, older person and pregnant women are most at the risk.
- Ingestion of excessive Cd^{2+} replaces Zn^{2+} ion at the key enzymatic sites causing metabolic disorder.
- Cd^{2+} leads to decalcification (through competitive inhibition) in bones and the bones become fragile.
- At high level, Cd^{2+} causes kidney problems, anemia and bone marrow disorder.

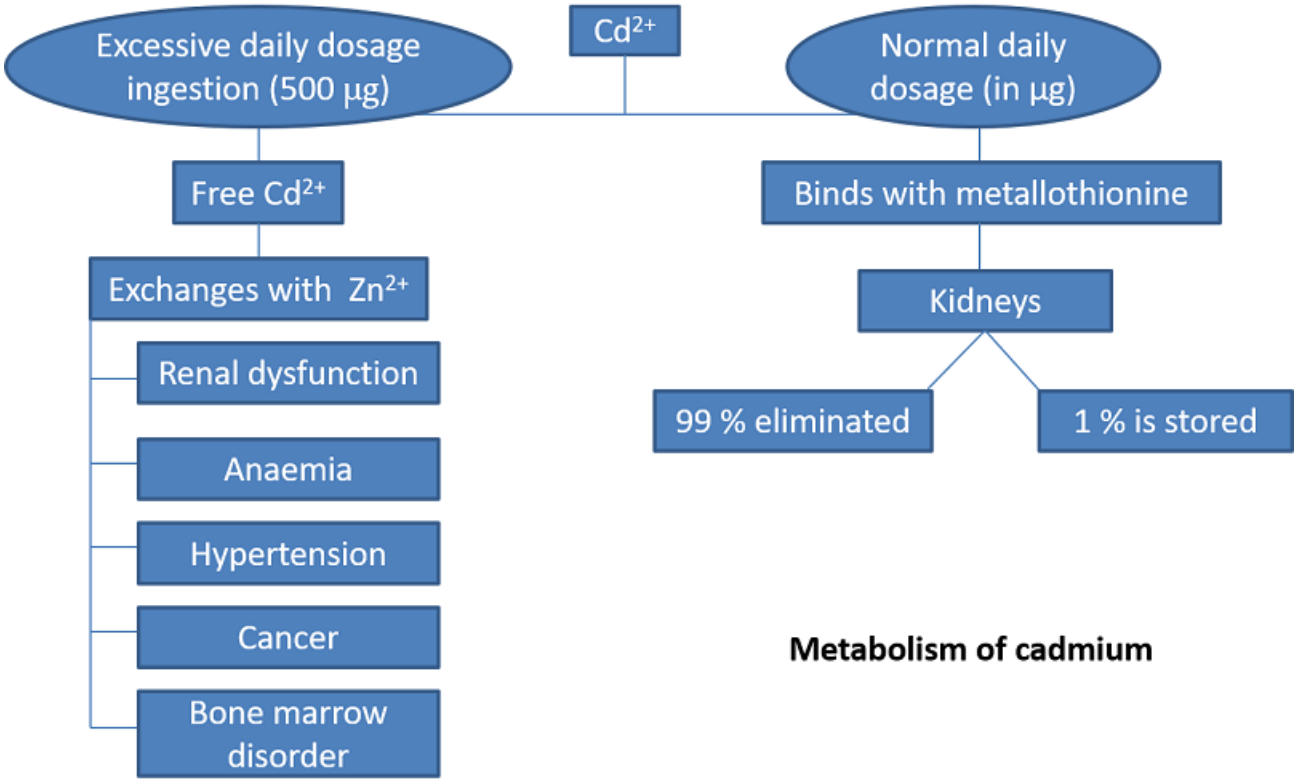
- An outbreak of Cd poisoning occurred in Japan in the form of itai itai or “Ouch ouch” disease where the victims suffered from fragile bones. It is also accompanied by renal dysfunction.
- Respiratory and pulmonary damages occur on breathing Cd vapor or particulates.



Summary of Cd-poisoning



Bio amplification of Cd



Metabolism of cadmium

Exercises

1. The metal that is non prevalent in biology

(a) Pt (b) Mn (c) Co (d) Ni

2. The metal ions with highest mobility in biological media are

(a) Zn(II)n & Ni(II) (b) Fe(II) & Cu(II) (c) Na(I) and K(I) (d) Mg(II) and Ca(II)

3. Toxic properties of Hg and its compounds are due to their

(a) High affinity for reaction with thiols (b) Interference with oxygen transport

(c) Binding to histidines (d) Inhibition of Vit B12 synthesis

4. Which metal are very toxic?

(a) Hg, Cd, As, Fe, Cr(VI) (b) Hg, As, Pb, Cr(VI), Cd

(c) Cd, Hg, Pb, Zn, Co (d) As, Pb, Pt, Au, Mg

5. How is Hg released into the environment? (more than one option)

(a) Coal burning and fungicides (b) batteries and paint

(c) Tube light and fungicides (d) coal burning

6. Which metal is used for nitrogen fixation

(a) W, Cu (b) Ni, Ti (c) V, Mo (d) only Mo

7. Which metal deficiency causes anemia

(a) Fe (b) Co (c) Cu (d) All

8. Which of the following complex is used for the treatment of breast cancer?

(a) Ca-EDTA (b) Ni-EDTA

(c) cis-platin (d) Carboplatin

9. Which of the following element causes the Alzheimer's disease

(a) Pb (b) Cr (c) Pd (d) Al

10. Which of the following ,metal disbalance cause the Wilson disease?

(a) Cu (b) Zn (c) Fe (d) Na