

BIOINORGANIC CHEMISTRY

Elements in body

Consider the content of the elements in the body of an average healthy person (weighing 70 kg). It has been established that out of 70 kg man's weight

Oxygen accounts for (more than half the total weight)	45.5 kg
Carbon accounts for	12.6 kg
Hydrogen accounts for	7.0 kg
Nitrogen accounts for	2.10 kg
Phosphorus accounts for	700 g

Total weights of metals in gms

Calcium	1050.0
Potassium	140.0
Sodium	105.0
Magnesium	35.0
Iron	4.2
Zinc	2.3

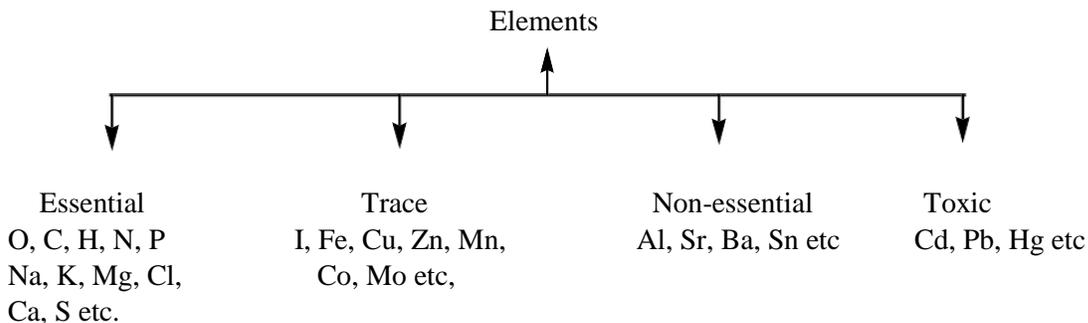
Geochemical effects on the distribution of metals

All the most essential elements, except Mo are fairly abundant in the earth's crust. Al (8.2%), Si (28.2%), Ti (0.57%) and Zr (0.02%) are although abundant but these are not essential elements. Because all these form insoluble oxides at biological pH values and do not form stable complexes with complexing agents of biological significance.

No common element is toxic at levels normally encountered though almost anything can be harmful at too high levels. All the well known toxic elements, which are currently of much concern in environmental pollution problems, are extremely rare in abundance in the earth crust.

As ($\sim 2 \times 10^{-10}\%$), Pb ($\sim 1.3 \times 10^{-10}\%$), Cd ($\sim 2 \times 10^{-10}\%$) and Hg ($\sim 5 \times 10^{-10}\%$).

Classification of elements according to their action in the biological system



Essential elements are absolutely essential or necessary for life processes. Trace elements are also necessary for life processes.

Non-essential elements are not essential. If they are absent other elements may serve the same function.

Toxic elements disturb the natural functions of the biological system.

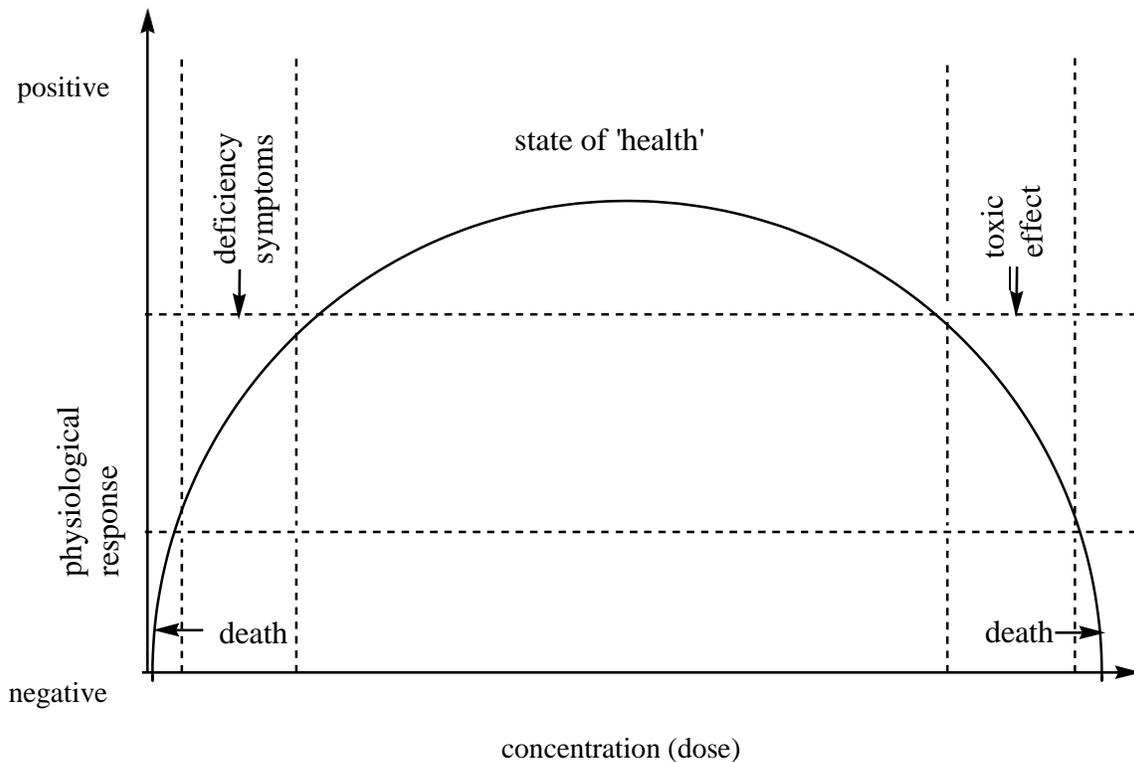
METAL IONS IN THE BIOLOGICAL SYSTEM

Metal ions their excess and deficiency

Concentration of metal ions in human being's system is controlled within very fine limits. This control is generally exercised by certain biological complexing agents. The deficiency or excess of metal ions causes disorder, which leads to various diseases.

Calcium

Calcium is a critical element in all animals and man. The primary dietary source of Ca is milk (65-76%), with smaller amounts derived from meat, fish and eggs (5-10%), and still less from non-dairy foods such as nuts, fruits, beans etc. Dietary deficiency of Ca is not a common problem in nations with high dairy product and protein intake, particularly since normal individuals can regulate intestinal absorption and renal conservation mechanism with great precision. Hence, human health problems related to geochemical distribution of Ca, its entry into the human food chain and its bio-availability are relatively uncommon. Exceptions include very poor diets (such as those low in milk and animal proteins or unusual physiologic, other illness, such as intestinal malabsorption). In case of excess of Ca, it comes in to the blood as Ca is rejected by cell and its salts are not are not soluble. So excess of Calcium leads to the formation of stones, hardening of arteries, and cataracts in the eye.



Magnesium

Magnesium, an abundant element in the earth's crust, is vital to both plant and animal life. Chlorophyll pigment in plants is a Mg-porphyrin complex. All enzymatic reaction in animals and men that are catalyzed by ATP require Mg as a cofactor. Oxidative phosphorylation, DNA transcription, RNA function, protein synthesis and critical cell membrane functions are all dependent upon optimal Mg concentrations. Dietary sources high in Mg include nuts, sea foods, legumes and vegetables, meat is intermediate in Mg content.

Potassium

An adult human has approximately 140 g K of which >90% is both intracellular and exchangeable (K is the predominant cation in intracellular water) since muscle contains most of the body's intracellular water, it also contains most of the K. Since K is found in most animal and vegetable foods, dietary deficiency is exceedingly rare except under unusual conditions (such as diets very high in refined sugars, alcoholic individuals deriving most of their calories from low-K alcoholic beverages in the states of starvation etc.).

Sodium

Sodium is the predominant extracellular cation in animals and man. An adult human has about 105 g Na, about 24% is located in bone and about 65% in extracellular water. Sodium ion equilibrium is maintained primarily by the kidney, the key organ in water and electrolyte balance. Sodium chloride (salt) is the predominant dietary source. Although excessive dietary Cl appear to have no significant ill effect on health, there is much evidence that excessive Na intake results in elevated blood pressure (hypertension) and that reduces Na intake or increased K intake helps to reduce high blood pressure.

Cobalt

Cobalt is an essential element for humans, but its pathway through the food chain to human being remain elusive. Only a little over 1 mg Co is present in an adult human. In man dietary Co deficiency is only likely among strict vegetarians or when the intrinsic factor from the stomach that facilitates decreased as in pernicious anaemia.

Zinc

An adult has about 1.5-3.0 g Zn with the largest amounts being in liver and bone. There is evidence that Zn concentrations in blood and several tissues vary considerably in response to many stimuli. Zinc appears to be critical in many functions. Human Zn deficiency in an inherited form in infants is termed acrodermatitis enteropathica and is characterized by behavioral disturbances, diarrhoea, hair loss and severe peri-orificial skin rash, all of which respond with remarkable promptness to Zn administration. Similar syndromes have now been reported many times with penicillamine treatment of other disorders, presumably due to chelation of Zn, as well as during total parenteral nutrition when Zn was not added to the nutritional solutions for even as short a time as two weeks.

Molybdenum

The essentiality of Mo in animals and human beings is assumed from its presence in the metalloenzymes xanthine oxidase and aldehyde oxidase. Mo is also part of the enzyme sulphite oxidase, an inherited deficiency of which cause severe neurologic disorders and early death in humans. However, no naturally occurring Mo deficiency has ever been documented in animals or man, even though several animal deficiencies have been produced experimentally, particularly by using the Mo antagonist. Molybdenum is present in very small quantities. Molybdenum appears to be readily absorbed from the GI tracts and excreted primarily through the kidneys (though human studies are lacking). In tissues with higher concentration, such as bone, liver and kidney the Mo content can be varied with dietary intake. There is evidence that dietary Mo affects Cu metabolism in animals and man, higher Mo intakes causing mobilization and excretion of Cu. These effects can be elicited in man even with naturally occurring dietary sources of Mo. Since Mo concentrations in grains and vegetables varies enormously (differences up to 500 times) and varies with soil content the possibility of Mo-induced Cu deficiency in man is conceivable, though not reported.

Chromium

The designation of Cr as an element essential to animals and man is quite recent. Insofar as is known, the major biological function of Cr is an integral part of an organic complex originally isolated from yeast termed "glucose tolerance factor" (GTF). This complex apparently includes one Cr (III) ion and two nicotinic acid molecules and may coordinate with three amino-acid molecules, probably glycine, cysteine and glutamic acid. Experimental data indicate that GTF functions in conjunction with insulin, and may in fact aid in binding insulin to sites of action. Other activities apparently include a lowering of serum cholesterol and triglycerides. An adult human has about 6 mg Cr. Trivalent Cr is absorbed in the upper gastrointestinal tract, but only in very small amounts (hexavalent Cr is better absorbed, but only trivalent Cr is biologically active as an essential element). Trivalent Cr as GTF is apparently absorbed much better. Thus conversion to GTF in the gastrointestinal tract may be important, and may vary with age of the individual. Chromium in excess amounts can be quite toxic, dependent upon the chemical species of Cr(III) is much less toxic than the hexavalent form. Chromium is a known carcinogen and toxic metal present abundantly in tannery effluents in India. As an estimate, about 80-90% of the tanneries use chromium as a tanning agent. Of this quantity, the hides take up only 50-70%, while the rest is discharged as effluent. This rest amounts to nearly 75, 000 tonnes per day. Today, the tannery industry mushrooming in North India has converted the Holy Ganges River into a dumping ground. Several analyses reveal high concentrations of chromium even in supposedly "treated" effluents. The residues can be traced even in crops cultivated with water taken from the river. The Department of Environment has identified the tannery industry as the 'biggest pollutant'

across the country. Electroplating can also release chromic acid spray and air-borne Cr trioxide, both of which can result in direct damage to skin and lungs.

Copper

Normal adult human has about 100-110 mg Cu, highest concentrations are found liver, kidney, heart and brain. The prototype functional deficiency of Cu in humans is an X-linked inherited disorder called Menke's syndrome (Kinky or steely hair syndrome). Cu insufficiency was first suspected by analogy with abnormal wool in Cu-deficient sheep. The defect appears to be decreased gastrointestinal absorption and /or cellular utilization of Cu. The essentiality of Cu is the consequence of its role in metalloenzymes involving several critical biochemical pathways. Copper is accumulated in a number of tissues but in particular is found in the liver, brain and kidney which leads to liver and kidney failure and various neurological abnormalities. Death results if the condition is not recognized and treated.

Iron

The average human adult has about 4-5 g Fe. Of this amount, about 60-70% is present in haemoglobin in red blood cell, 3-5% is in muscle myoglobin, 15% is bound to the Fe storage cellular protein, ferritin, 0.2% occurs as a component of critical respiratory enzymes and 0.004% is bound to the serum transport protein transferrin. Iron deficiency causes anemia because red cells of blood containing less hemoglobin than in normal condition. Acute iron poisoning leads to vomiting, pallor, shock, circulatory collapse and coma. Chronic conditions are also known in which iron is deposited in tissues and organs of the body. This condition is known as siderosis.

Toxicity:

Mechanism of the toxicity of metals is very complicated. Generally toxicity of metals may result from one of the following:

- i) Blocking the essential biological functional groups of biomolecules such as enzymes. Amino acid residues like serine is –OH functional group, cysteine is –SH group and histidine –N group often constitute the active sites of enzymes. A toxic metal ion may bind with these functional groups and block the activity of the enzyme.
- ii) Displacing the essential metal ions from biomolecules. A biomolecule with a foreign metal ion loses its activity.
- iii) Modifying the active conformation of biomolecules. Biomolecules are having specific active conformations and if this active conformation is lost due to the coordination of a metal ion, the activity of the biomolecule is lost.

Toxic Metals**Mercury:**

Sources of Mercury pollution are industrial waste, mining (as mercury is trace component of many minerals), pesticides, coal & lignite (containing about 100 ppb of Hg). It is a well known toxic metal came to lime light after the incidence of “Minamata disease” in 1953-60 in Japan. One hundred eleven cases of mercury poisoning were reported who had eaten mercury contaminated fish from Minamata Bay. Among them 45 people died. The sea fish were found to be containing 27-102ppm of Hg in the form of methyl mercury. The mercury source was the effluent (Hg containing catalyst wastes) from a vinyl chloride plant (Minamata Chemical Company) releasing into the bay. This was followed by more tragic report of mercury poisoning from Iraq in 1972, where 450 villagers died after eating wheat which had been dusted with mercury containing pesticides. These two tragic events boosted the awareness of mercury as pollutant; and ultimately resulting in its being studied more extensively than any other trace elements. Mercury can be toxic by ingestion or inhalation, but the toxicity depends upon the chemical form. Soluble inorganic mercury salts are highly toxic.

Reason for Toxicity: Toxicity of mercury is based on the strong affinity for the deprotonated forms of thiol ligands such as Cysteine; therefore, thiols, RSH, with sulfhydryl group, -SH are also called mercaptans (Mercurium captans). So Hg (II) binds strongly with the thiol group of proteins and enzymes and this binding changes the confirmation of protein about the active site. Mercury is a soft acid and –S of –SH group is a soft base so strong interaction between mercury and -SH group can be explained on the basis of stronger soft-soft binding.

Cadmium:

The source of Cd pollution in urban areas are metallurgical plants, Cd plating and battery fabricators. Acute Cd poisoning leads to nausea, salivation, vomiting, diarrhea and abdominal pain. Cd deposition tends to be cumulative in the kidney with lower

concentrations in the liver. Another characteristics of Cd poisoning is brittleness of bones. Cd occurs in nature in association with Zn minerals. A severe outbreak of chronic Cd poisoning occurred along the Jintsu river of North-West Japan and was known as Itai- Itai or ouch-ouch disease. Over 20 year period around 100 people died. In 1961 Cd was found to be the cause. The region was due to a old disused zinc mine and river water which was containing Cd used for irrigation of rice and people died after eating the rice. **Reason for toxicity:** Cd is similar to zinc. Therefore Cd (II) can displace Zn (II) in many zinc enzymes. Like Hg (II), Cd (II) also binds strongly with the –SH groups of Cysteine residues of enzymes e.g., Carbonic anhydrase, dipeptidase, carboxy peptidase etc. Cd (II) like other toxic metal ions effects the active confirmation of biomolecules due to the strong binding.

Lead :

Sources of pollution : Battery industry is the largest single user of lead. But leaded petrol accounts for more than 20% of total lead consumed per year and 90% of lead released to atmosphere is from gasoline exhaust. The triethyl lead cation, is formed from tetraethyl lead by the dissociation of a carbanion. Toxicity; of this organometallic cation results from the permeability of membranes, including the very discrimination blood-brain barrier causing several disorders of central and peripheral nervous system (cramps, paralysis, loss of coordination). One of the characteristic symptoms of lead poisoning is anemia.

Reason for toxicity: Like Hg (II) and Cd (II) lead inhibits SH-enzyme but less strongly. Major biochemical effect of Pb is its interference with heme synthesis by inhibiting several of key enzymes involved in the overall process of heme synthesis.