Geochemical effects on the distribution of metals

All the essential elements, except Mo are fairly abundant in the earth's crust. Although Al (8.2%), Si (28.2%), Ti (0.57%) and Zr (0.02%) are abundant, these are not essential elements. Since all these elements form insoluble oxides at biological pH and do not form stable complexes with complexing agents of biological significance, they are non-toxic at normal levels. Though they can be harmful at very high levels. All the well known toxic elements, are extremely rare in the earth's crust: As (~ 2×10^{-4} %), Pb (~ 1.3×10^{-3} %), Cd (~ 2×10^{-5} %) and Hg (~ 5×10^{-5} %).

Average elemental composition of a human body

Element	Symbol	Percentage in Body
Oxygen	O	65.0
Carbon	C	18.5
Hydrogen	H	9.5
Nitrogen	N	3.2
Calcium	Ca	1.5
Phosphorus	P	1.0
Potassium	K	0.4
Sulfur	S	0.3
Sodium	Na	0.2
Chlorine	Cl	0.2
Magnesium	Mg	0.1
Trace elements include boron (B), chromium (Cr), cobalt (Co), copper (Cu), fluorine (F), iodine (I), iron (Fe), manganese (Mn), molybdenum (Mo), selenium (Se), silicon (Si), tin (Sn), vanadium (V), and zinc (Zn).		less than 1.0

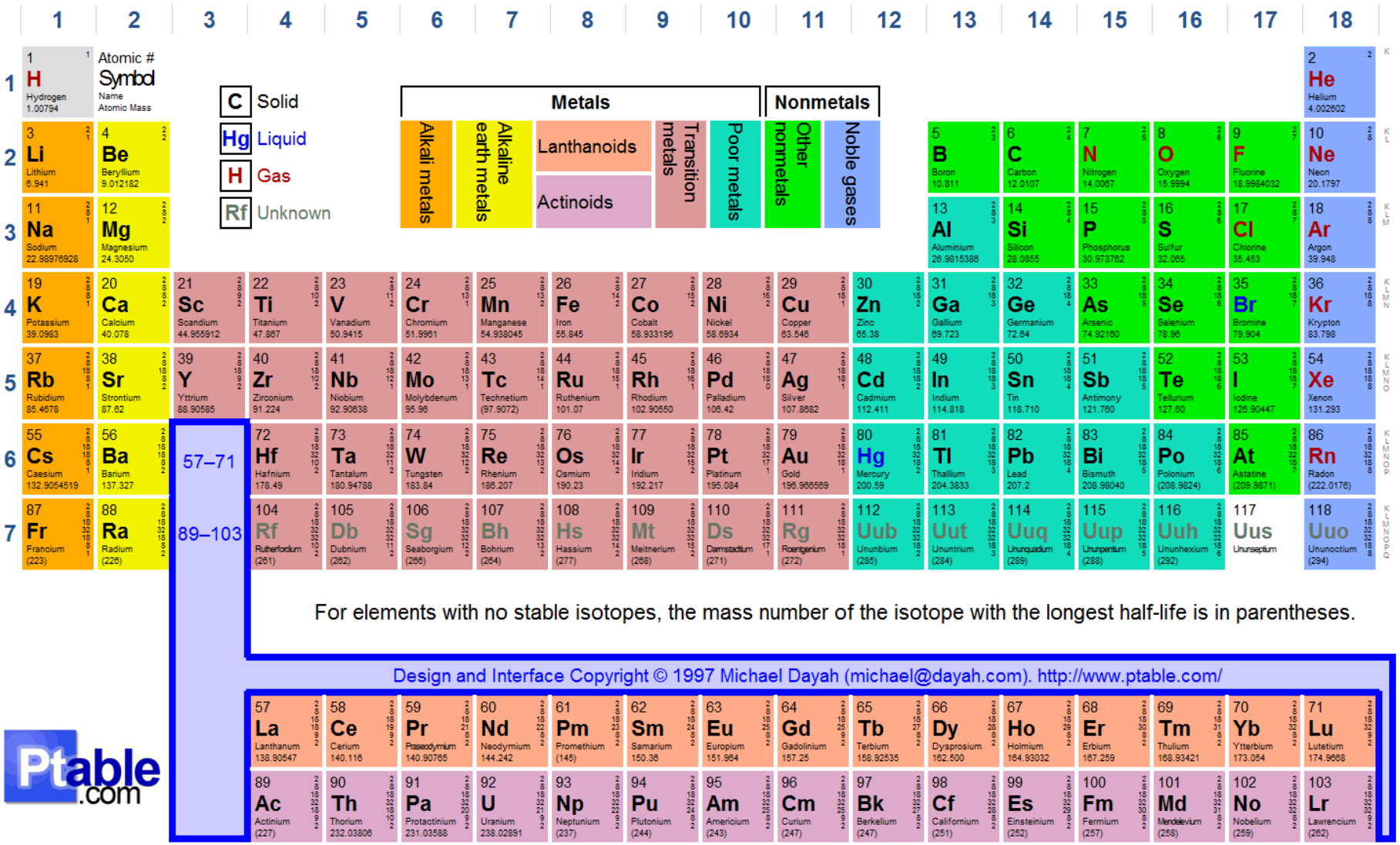
Occurrence and Availability of Inorganic Elements in Organisms

- The occurrence of the elements in organisms depends on external and endogenous conditions
- The high percentage of O and H reflect high content of water
- Calcium- The most abundant metal in body. Its main quantitative use being the stabilization of the endoskeleton
- The elements Si, Al and Ti, are abundant in the earth's crust, play only a marginal role in the biosphere. Reason :

➢ Under normal physiological conditions (pH ≈ 7), these elements in their usual high oxidation states exist as nearly insoluble oxides or hydroxides and are therefore not (bio)available.

- Mo, a rare element in the earth's crust but soluble at pH 7 as $MoO4^{2-}$ has been found as an essential element in many organisms.

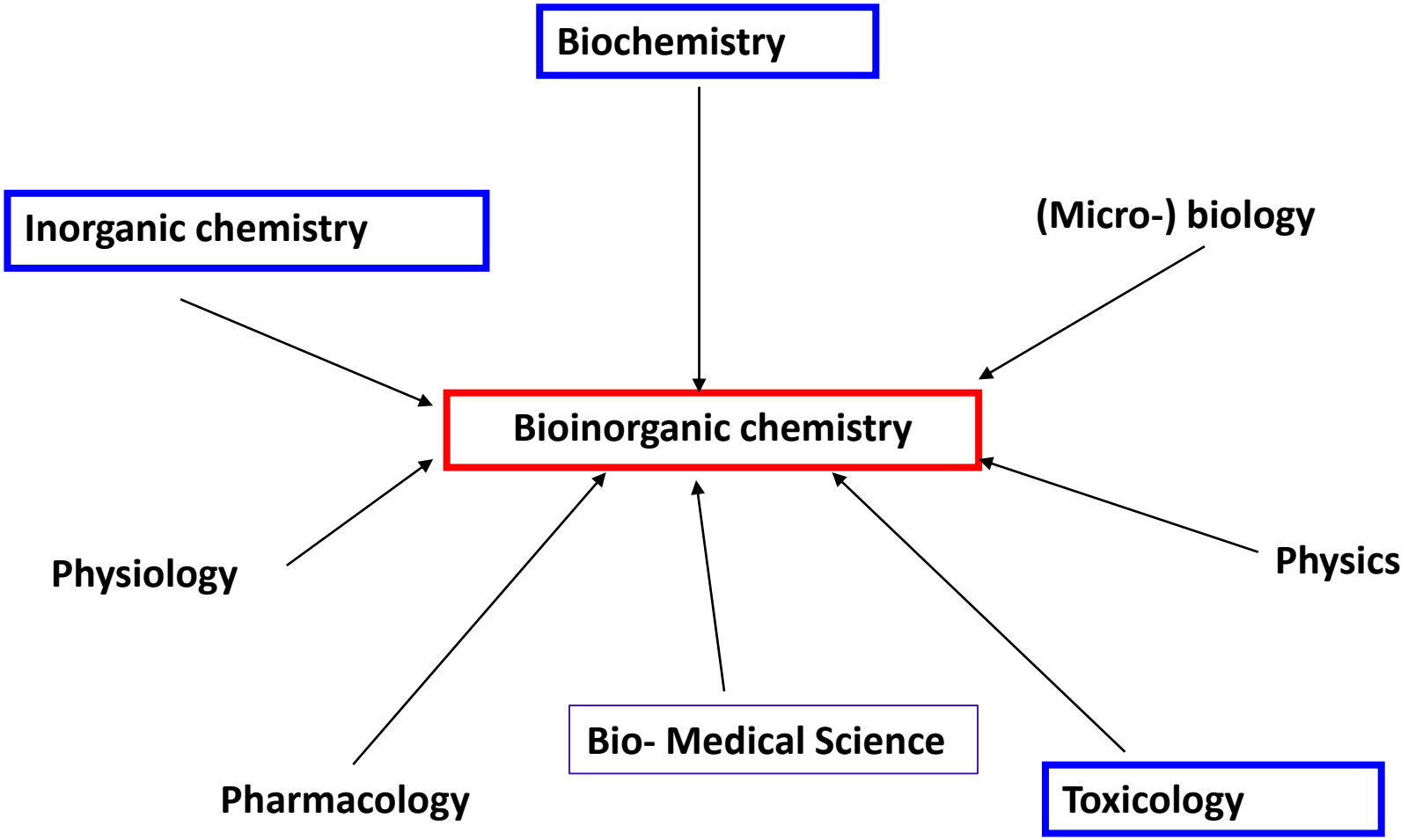
Periodic Table of Elements

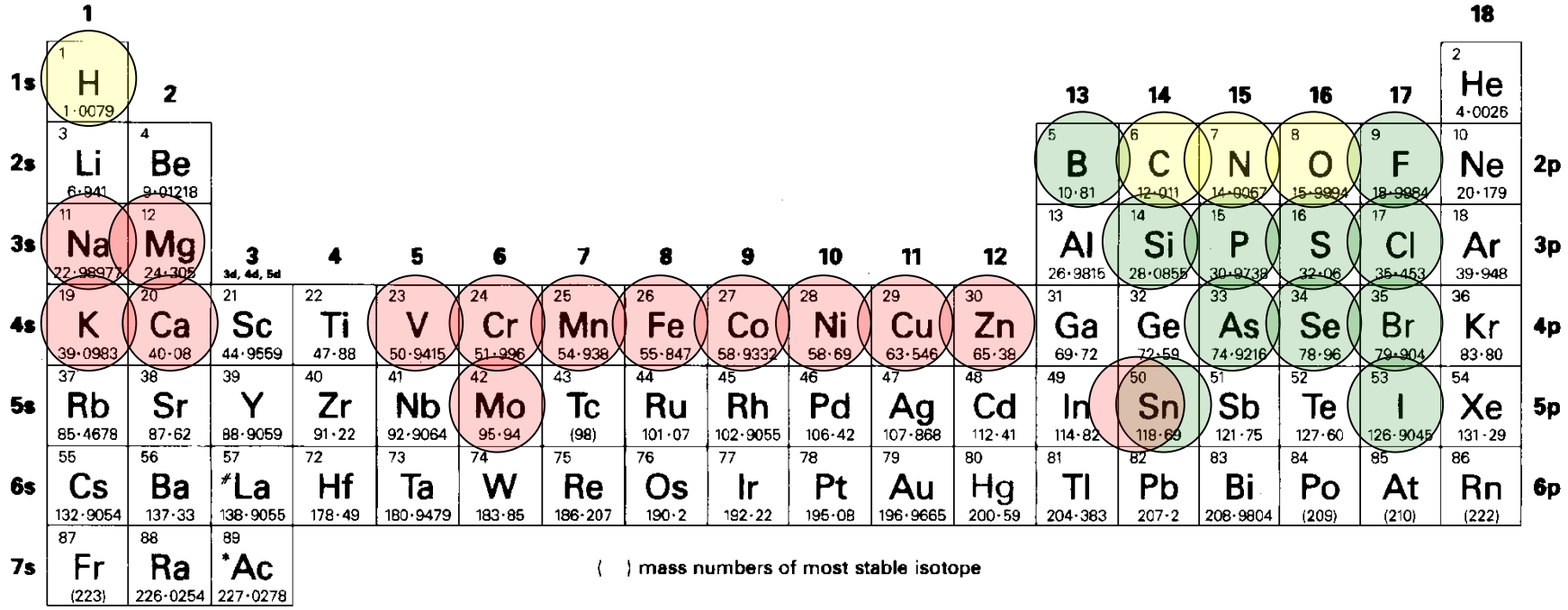


For elements with no stable isotopes, the mass number of the isotope with the longest half-life is in parentheses.

Ptable.com

Bioinorganic chemistry - Interdisciplinary Research field





LANTHANUM SERIES

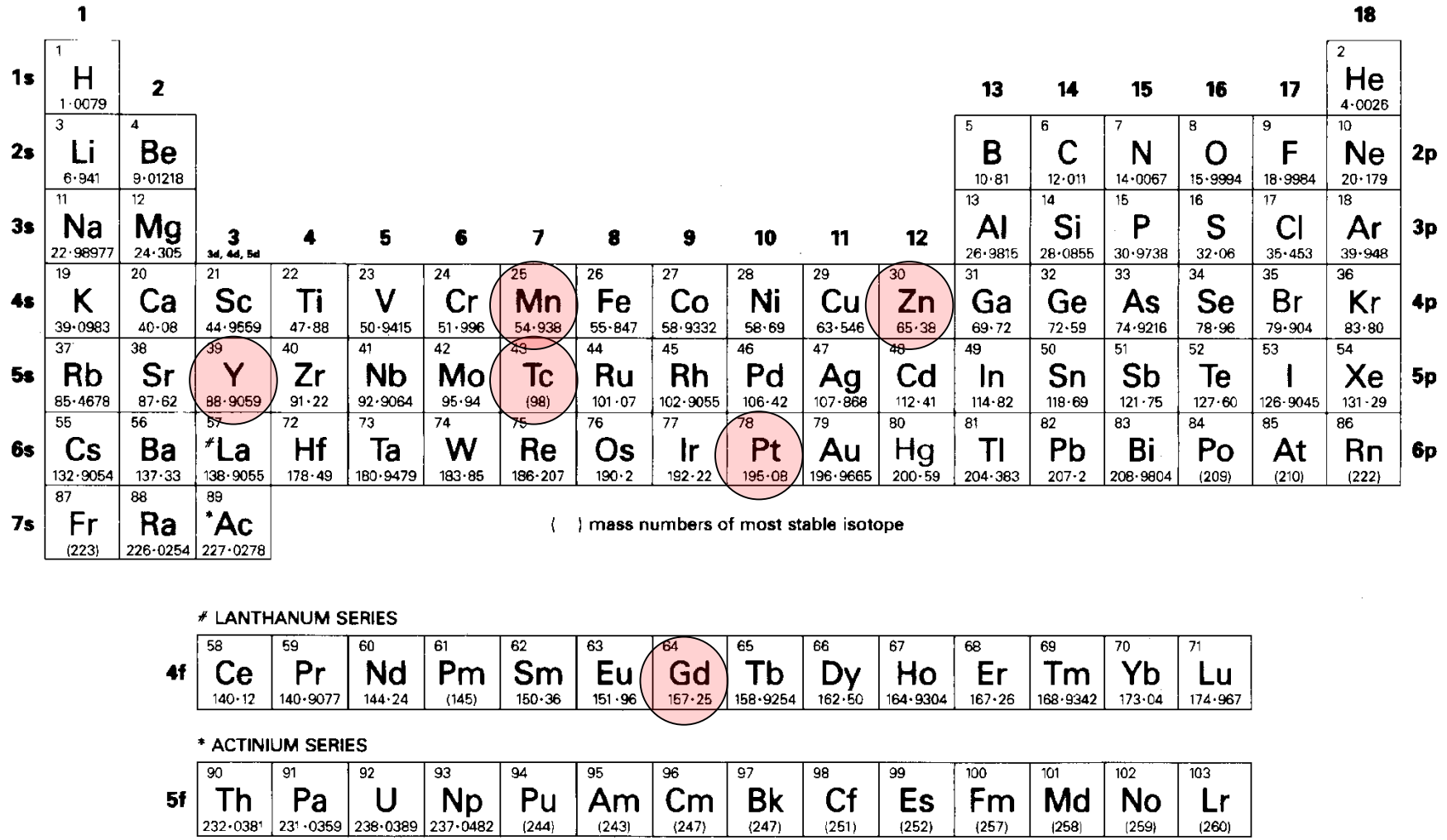
4f

58	59	60	61	62	63	64	65	66	67	68	69	70	71
Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
140·12	140·9077	144·24	(145)	150·36	151·96	157·25	158·9254	162·50	164·9304	167·26	168·9342	173·04	174·967

* ACTINIUM SERIES

5f

90	91	92	93	94	95	96	97	98	99	100	101	102	103
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr
232·0381	231·0359	238·0389	237·0482	(244)	(243)	(247)	(247)	(251)	(252)	(257)	(258)	(259)	(260)


1
18
1s
2
13
14
15
16
17
2s
2p
3s
3p
3
3d, 4d, 5d
4
5
6
7
8
9
10
11
12
4s
4p
5s
5p
6s
6p
7s
1 H 1·0079
2 He 4·0026
3 Li 6·941
4 Be 9·01218
5 B 10·81
6 C 12·011
7 N 14·0067
8 O 15·9994
9 F 18·9984
10 Ne 20·179
11 Na 22·98977
12 Mg 24·305
13 Al 26·9815
14 Si 28·0855
15 P 30·9738
16 S 32·06
17 Cl 35·453
18 Ar 39·948
19 K 39·0983
20 Ca 40·08
21 Sc 44·9559
22 Ti 47·88
23 V 50·9415
24 Cr 51·996
25 Mn 54·938
26 Fe 55·847
27 Co 58·9332
28 Ni 58·69
29 Cu 63·546
30 Zn 65·38
31 Ga 69·72
32 Ge 72·59
33 As 74·9216
34 Se 78·96
35 Br 79·904
36 Kr 83·80
37 Rb 85·4678
38 Sr 87·62
39 Y 88·9059
40 Zr 91·22
41 Nb 92·9064
42 Mo 95·94
43 Tc (98)
44 Ru 101·07
45 Rh 102·9055
46 Pd 106·42
47 Ag 107·868
48 Cd 112·41
49 In 114·82
50 Sn 118·69
51 Sb 121·75
52 Te 127·60
53 I 126·9045
54 Xe 131·29
55 Cs 132·9054
56 Ba 137·33
57 #La 138·9055
72 Hf 178·49
73 Ta 180·9479
74 W 183·85
75 Re 186·207
76 Os 190·2
77 Ir 192·22
78 Pt 195·08
79 Au 196·9665
80 Hg 200·59
81 Tl 204·383
82 Pb 207·2
83 Bi 208·9804
84 Po (209)
85 At (210)
86 Rn (222)
87 Fr (223)
88 Ra 226·0254
89 *Ac 227·0278
( ) mass numbers of most stable isotope
LANTHANUM SERIES
4f
58 Ce 140·12
59 Pr 140·9077
60 Nd 144·24
61 Pm (145)
62 Sm 150·36
63 Eu 151·96
64 Gd 157·25
65 Tb 158·9254
66 Dy 162·50
67 Ho 164·9304
68 Er 167·26
69 Tm 168·9342
70 Yb 173·04
71 Lu 174·967
* ACTINIUM SERIES
5f
90 Th 232·0381
91 Pa 231·0359
92 U 238·0389
93 Np 237·0482
94 Pu (244)
95 Am (243)
96 Cm (247)
97 Bk (247)
98 Cf (251)
99 Es (252)
100 Fm (257)
101 Md (258)
102 No (259)
103 Lr (260)

Evolution of life : Essential Elements

Earth solidified ~ 4 billion years ago

81 stable elements

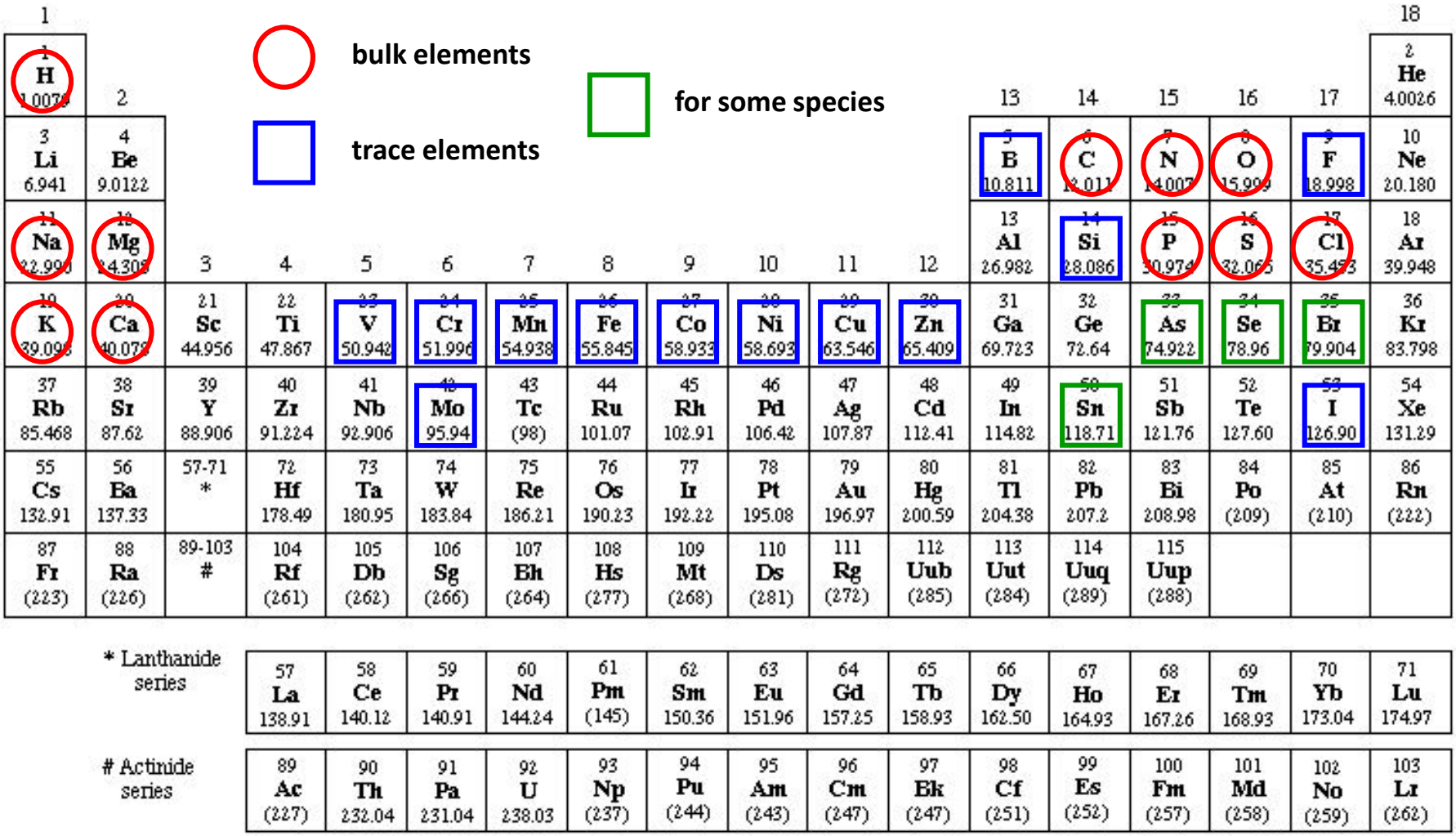
Elements of the living organism:

1. Elements in large scale: 11 elements
   H, C, N, O, Na, Mg, P, S, Cl, K, Ca

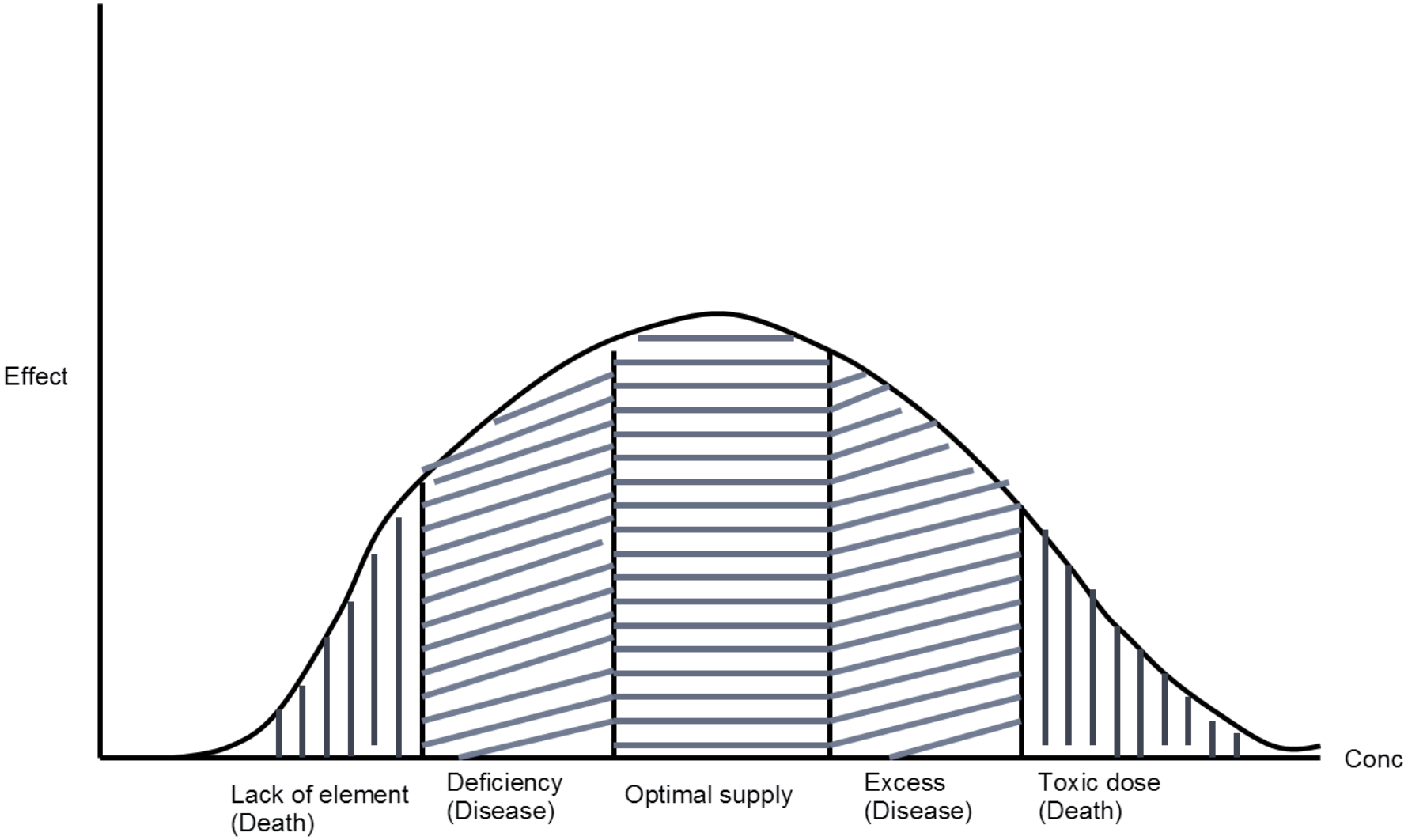
2. Elements in small scale: 7 elements
   Mn, Fe, Co, Cu, Zn, I, Mo

3. Elements of a few species: 7 elements
   B, F, Si, V, Cr, Se, Sn

Periodic Table



Concentration and Physiological Effect



Some fundamental metal sites in metalloproteins

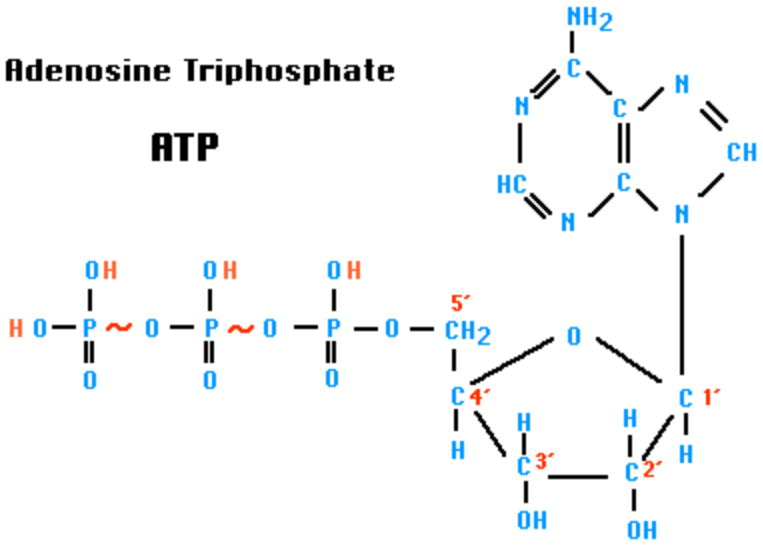
Metal site	Function
1. Metal complexes of porphyrins and corrins	
- Iron porphyrins	
= Hemoglobin & Myoglobin	O_2 transport
= Cytochromes	Redox catalysts
- Vitamin B_{12} = Cobalt corrinoid	Radical catalyst Methyltransferase
2. Bridged bimetallic complexes	
- Fe_2 clusters	
= Hemerythrin	O_2 transport
= Methane Monooxygenase	Hydroxylase
= Ribonucleotide Reductase RR2	Radical generation
- Cu_2 clusters	
= Hemocyanin	O_2 transport

Some fundamental metal sites in metalloproteins Cont..

- Mn_2 clusters	
= O_2-evolving complex	Photosystem II
= Mn-Catalase	H_2O_2 disproportionation
- Zn_2 clusters	
= Zinc aminopeptidases	Peptide cleavage
- Ni_2 clusters	
= Urease	Hydrolysis of urea
3. Fe-S clusters	Electron transfer
4. Mo-pterin	Xanthine oxidase
3. Zinc fingers	DNA binding

ATP = adenosine triphosphate

- A nucleotide (ribose sugar, adenine base and three phosphate groups)
- **Energy currency** of the cell, providing the energy for most of the energy-consuming activities
- It regulates many biochemical pathways



Na^+/K^+ Pump

- Found in membranes of cells.
- Produces electrical and chemical gradient across a cell membrane.
- It plays a very important role in nerve cell membranes.
- Transmission of nerve impulses.
- Channel = tunnel-like trans membrane protein: Na^+-K^+ ATPase
- K^+ inside a cell
- Na^+ outside a cell
- Cell surface membranes pump Na^+ ions out of cell and K^+ in.

K^+

- Enzyme activator
- Conformation of
  - proteins
  - RNA (replication)
- Secretion of gastric acid
- Transmembrane potentials!

Complexes of alkali metals (Na^+, K^+)

Cyclic antibiotics

- Valinomycin
- Monactin
- Nonactin

- polyethers
- cryptands

} synthetic

Alkaline Earth Metals

Mg^{2+}

- Plants → chlorosis

CHLOROPHYLL

- nervous system (tetany)
- active transport (intracellular)
- enzyme activator (e.g. ATP-ase)
- Ca^{2+} antagonist

Ca^{2+}

- Inhibits Mg^{2+}-activated enzymes
- Extracellular: clotting (10^{-3}M)

$$\text{prothrombin} \xrightarrow{Ca^{2+}} \text{thrombin-fibrinogen-fibrin}$$

Fe, Cu, Mo:

Electron-transfer

Redox proteins and enzymes

Oxygen carrying proteins

Nitrogen fixation

Zn:

Metalloenzymes

Structure promoters

Lewis acid

Not a redox catalyst!

Other metal ions: less well defined and more obscure roles

In human body

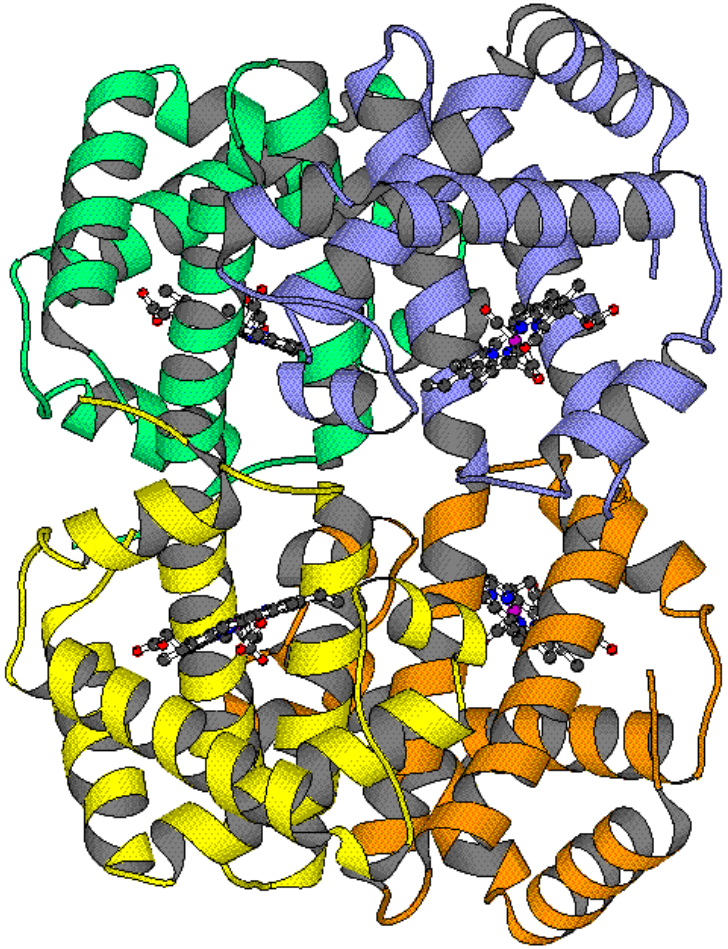
75% Hem-iron

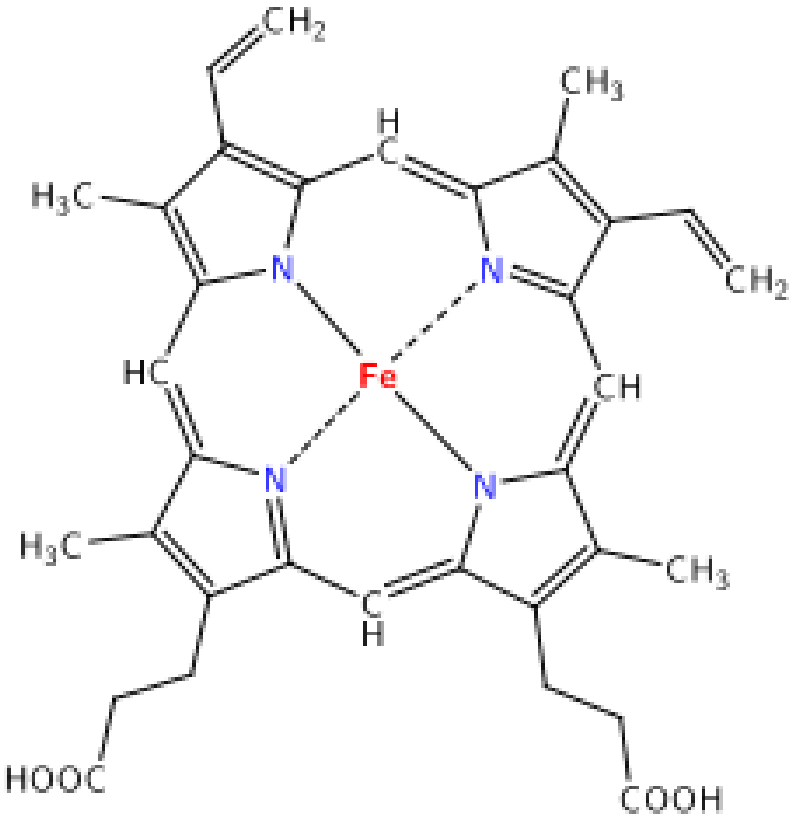
- Hemoglobin
- Myoglobin
- Cytochromes
- Oxidases, P-450

25% Non-hem-iron

- Rubredoxins
- Ferredoxins

Hemoglobin





Binding of O_2 alters the structure

Cu(I), Cu(II)

Plants
Animals

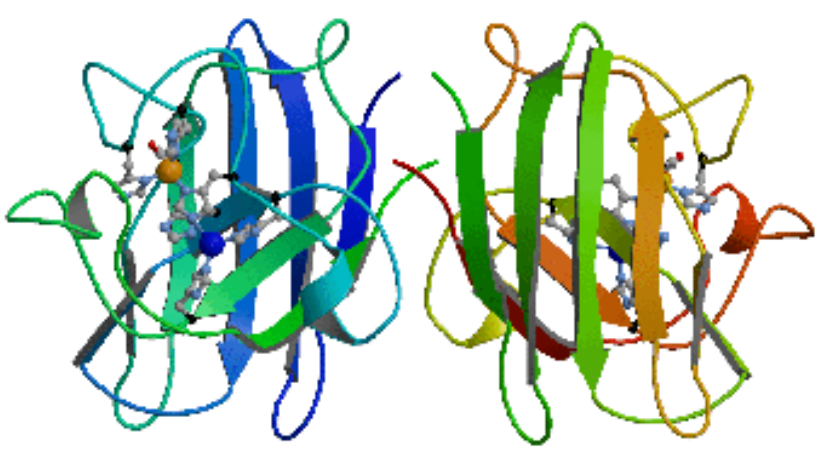
Electron transfer
O_2-carrying

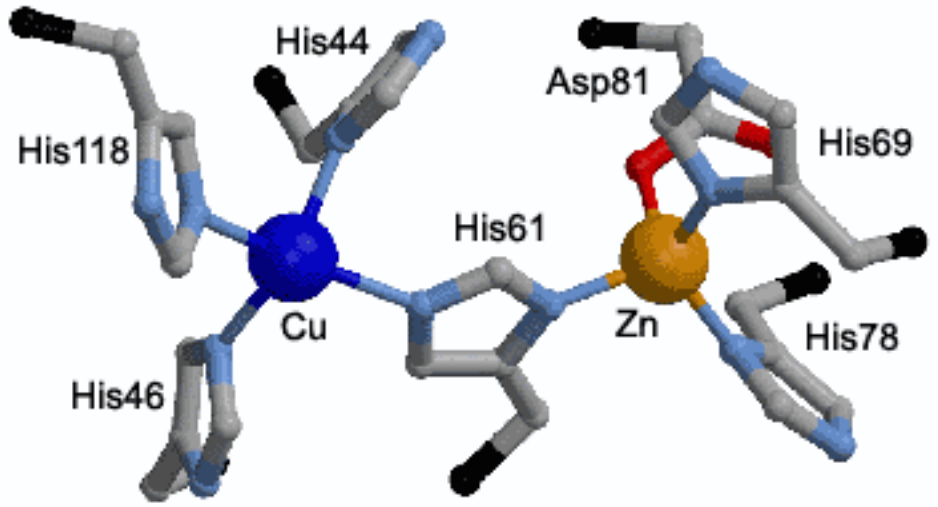
Protection of DNA from O_2^-

Cu-proteins and enzymes

- Cytochrome oxidase — $O_2 \rightarrow H_2O$
- Tyrosinase, phenol oxidase — ox. of phenols
- Ceruloplasmin — Fe(II) → Fe(III)
- Blue proteins — Electron transfer
- Superoxide dismutase — Elimination of O_2^-
- Hemocyanin — O_2 transport

Superoxide Dismutase





$$SOD\text{-}Cu^{2+} + O_2^{\cdot -} \Rightarrow SOD\text{-}Cu^{1+} + O_2$$

$$SOD\text{-}Cu^{1+} + O_2^{\cdot -} + 2H^{+} \Rightarrow SOD\text{-}Cu^{2+} + H_2O_2$$

Sodium

- Na+ is the major cation of extracellular fluid
- Maintenance of electrolyte balance and fluid balance
- The regulation of the osmotic pressure inside the cell
- The transmission of nervous pulses
- Maintenance of electrolyte balance and fluid balance

Deficiency of Sodium

- A low sodium level in the blood (**Hyponatraemia**) may result from excess water or fluid in the body, diluting the normal amount of sodium so that the concentration appears low
- This can be due to chronic conditions such as kidney failure and congestive heart failure
- Hyponatraemia can also result when sodium is lost from the body or when both sodium and fluid are lost from the body - for example, during prolonged sweating and severe vomiting or diarrhoea

Deficiency of Sodium

- Medical conditions associated can be adrenal insufficiency, hypothyroidism, and cirrhosis of the liver.
- Treatment of hyponatraemia involves intravenous fluid and electrolyte replacement, medication to manage the symptoms of hyponatraemia, as well treatments for any underlying cause.

Potassium

- Potassium plays an important role in regulation of cellular electrolyte metabolism
- Electric signaling in cells
- Transport of essential nutrients, and enzymatic analysis
- In alliance with other (i.e., sodium and chloride ions), it contributes to overall electrolyte balance of virtually all living organisms
- It also assists in the conduction of nerve impulses

Deficiency of Potassium

- Low potassium level is a condition in which the amount of potassium in the blood is lower than normal.
- The medical name of this condition is **hypokalemia**.
- Common causes of low potassium level include: Antibiotics, diarrhea or vomiting, chronic kidney disease, eating disorders (such as bulimia), low magnesium level, sweating.
- Mild Potassium deficiency can lead to constipation, feeling of skipped heart beats or palpitations, fatigue, muscle damage, tingling or numbness
- A large drop in potassium level may lead to abnormal heart rhythms, especially in people with heart disease
- A very low potassium level can even cause heart to stop.

Magnesium

- Mg is an integral part of the molecule of chlorophyll
- Prosthetic ion in enzymes that hydrolyze and transfer phosphate groups
- Essential for energy- requiring biological functions such as
  - Membrane transport
  - Generation and transmission of nerve impulses
  - Contraction of muscles
  - Oxidative phosphorylation
- Essential for the maintenance of ribosomal structure and protein synthesis

Deficiency of Magnesium

- Low magnesium is known in research circles as the silent epidemic of our times
- Many of the symptoms of low magnesium are not unique to magnesium deficiency, making it difficult to diagnose
- **Classic "Clinical" Symptoms** : Tics, muscle spasms and cramps, seizures, anxiety, and irregular heart rhythms are among the classic signs and symptoms of low magnesium
- **"Sub-clinical" or "Latent" Symptoms** : These symptoms are present but concealed by an inability to distinguish their signs from other disease states.

  They can include migraine headaches, insomnia, depression, and chronic fatigue, among others.
- Beginning magnesium therapy and magnesium supplements as soon as possible

Calcium

- It acts at intercellular, extracellular and intracellular sites
- It can modulate the excitability of cellular surface membranes and the transport of material along nerve fibres
- It can strengthen the mechanical properties of a tissue and stabilize enzymes
- It acts as a liaison between excitation and muscular contraction and also between excitation and secretion
- It plays a role in fertilization and in mitosis

Deficiency of Calcium

- **Hypocalcaemia** is the presence of low serum calcium levels in the blood
- It can be caused due to
  - A low level of parathyroid hormone (hypoparathyroidism)
  - A low level of magnesium (hypomagnesemia), which reduces the activity of parathyroid hormone
  - Vitamin D deficiency
  - Kidney dysfunction (a common cause)
  - Inadequate consumption of calcium
- Symptoms include dry scaly skin, brittle nails, and coarse hair. Muscle cramps involving the back and legs are common.
- Over time, hypocalcemia can affect the brain and cause neurologic or psychological symptoms, such as confusion, memory loss, delirium, depression, and hallucinations.
- Calcium and vitamin D supplements may be used

Zinc

- Zinc takes part in the catalytic function of many metalloenzymes.
- It plays a role in conformational stability.
- In zinc deficient animals protein synthesis is disturbed.
- Zinc takes part in
  - drug metabolism
  - in mobilizing vitamin A from the liver, and
  - in a system defending the organism against free radical damage.
- Zinc can protect the organism against cadmium toxicity
- In wound healing and tissue repair substitution of zinc is beneficial only if a zinc deficiency exists.
- For purposes of long term parenteral nutrition zinc should be added to the different infusion solutions.

Deficiency of Zinc

- Zinc deficiency in man is rare
- Zinc deficiency during growth periods results in growth failure.
- Epidermal, gastrointestinal, central nervous, immune, skeletal, and reproductive systems are the organs most affected clinically by zinc deficiency.
- In Iran and Egypt a syndrome of iron and zinc deficiency associated with anaemia, hepatosplenomegaly, dwarfism, and hypogonadism is known
- Clinical diagnosis of marginal Zn deficiency in humans remains problematic.
- Zinc deficiency is readily reversed by dietary supplements such as ZnS04, but high doses (>200 mg) cannot be given without inducing secondary effects of copper, iron, and calcium deficiency

The biological uses of Iron

FUNCTION	PROTEIN
Oxygen transport and storage	**Haemoglobin** in red blood cells transports oxygen in the blood, and **myoglobin** stores oxygen in muscles
Oxygen homeostasis	An iron-dependent **prolyl-hydroxylase** plays a critical role in the physiological response to hypoxia
Electron transport and energy production	**Cytochromes** and **dehydrogenases** are essential components of mitochondrial electron transport for ATP synthesis
Metabolism and detoxification	**Cytochromes** are also involved in the metabolism of biological molecules, drugs and pollutants
Antioxidant activity	**Catalase** and **peroxidases** metabolise hydrogen peroxide to reduce the risk of oxidative cellular damage
Beneficial pro-oxidant activity	**Myeloperoxidase** synthesises reactive oxygen species within neutrophils to aid bacterial cell killing
DNA synthesis	**Ribonucleotide reductase** is required for DNA synthesis

Deficiency of Iron

- **Iron deficiency** is the most common nutritional deficiency in the world
- Iron deficiency is due either to increased need for iron by the body (infants and pregnant women) or a decreased absorption or amount of iron taken in.
- Untreated iron deficiency can lead to iron deficiency anemia— a common type of anemia
- Signs of iron deficiency include fatigue, slow cognitive and social development during childhood, difficulty maintaining body temperature, decreased immune function, and glossitis (an inflamed tongue)
- Blood tests establish the diagnosis of iron deficiency
- Mild iron deficiency can be prevented or corrected by eating iron-rich foods and iron supplements like ferrous sulphate

Copper

- Copper plays an important role in our metabolism, largely because it allows many critical enzymes to function properly
- Copper is essential for maintaining the strength of the skin, blood vessels, epithelial and connective tissue throughout the body.
- Cu plays a role in the production of hemoglobin, myelin, melanin
- It also keeps thyroid gland functioning normally
- Copper can act as both an antioxidant and a pro-oxidant.

(Free radicals occur naturally in the body and can cause a number of health problems and diseases.)

- As an antioxidant, Cu scavenges or neutralize free radicals and may reduce or help prevent some of the damage
- When copper acts as a pro-oxidant at times, it promotes free radical damage and may contribute to the development of Alzheimer's disease

Deficiency of Copper

- Copper deficiency is a very rare hematological and neurological disorder because the daily requirement is low
- The most common cause of copper deficiency is a remote gastrointestinal surgery, such as gastric bypass surgery, due to malabsorption of copper, or zinc toxicity.
- Menkes disease is a genetic disorder of copper deficiency involving a wide variety of symptoms that is often fatal
- The deficiency in copper can cause many hematological manifestations, such as

➢ myelodysplasia,

➢ anemia,

➢ leukopenia (low white blood cell count) and

➢ neutropenia (low count of neutrophils, a type of white blood cell that is often called "the first line of defense" for the immune system)

- Copper deficiency has long been known for as a cause of myelodysplasia (when a blood profile has indicators of possible future leukemia development)

Toxicity of Metals

Two Classes of Toxic Metal Compounds

- **Toxicity due to Essential elements**

The presence of excess quantities of an essential metal can be as deleterious as insufficient amounts.

This can arise from accidental ingestion of the element or from metabolic disorders leading to the incapacitation of normal biochemical mechanisms that control uptake and distribution phenomena.

- **Toxicity due to Non-essential elements**

The entry of nonessential metals into thee cell through food, skin absorption, or respiration.

*The toxicities associated with this latter class have received much recent attention because of the public health risks of chemical and radioisotopic environmental pollutants

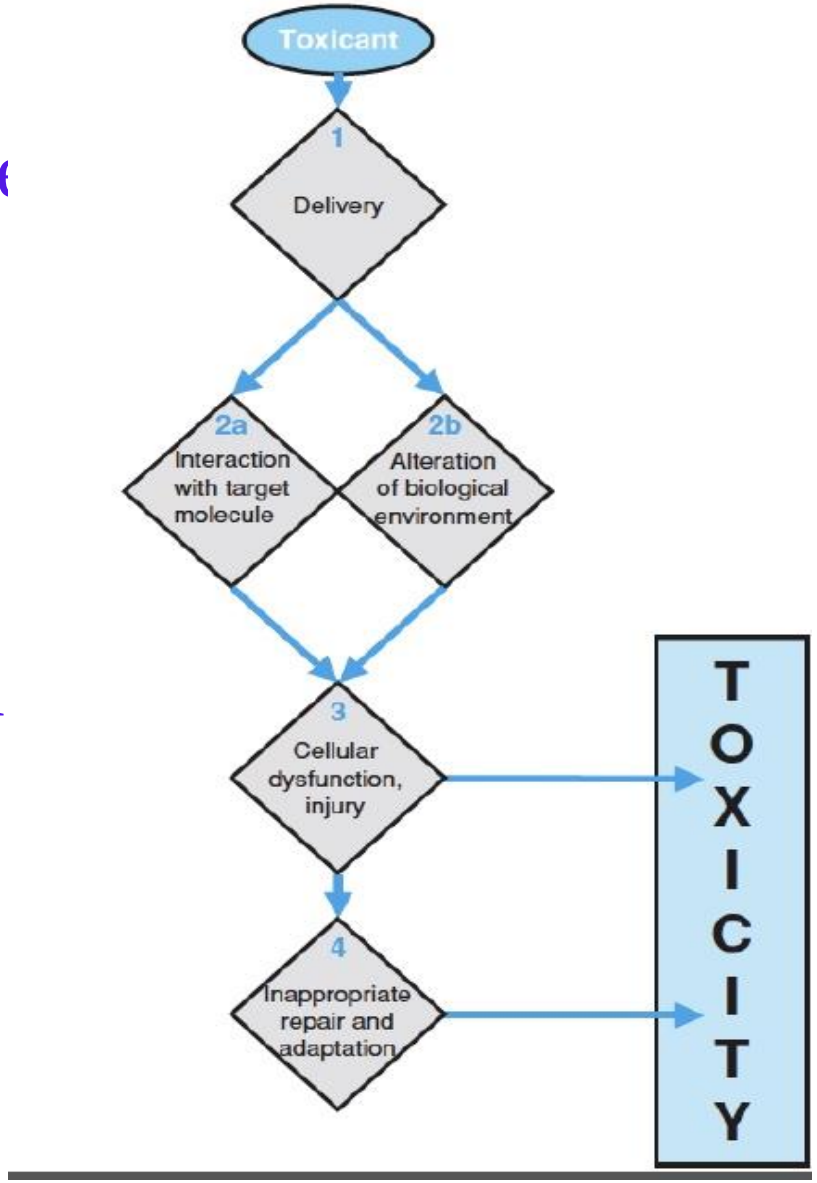
Mechanism of Toxicity

1.Delivery: Site of Exposure to the Target

2.Reaction of the Ultimate Toxicant with the Target Molecule

3.Cellular Dysfunction and Resultant Toxicity

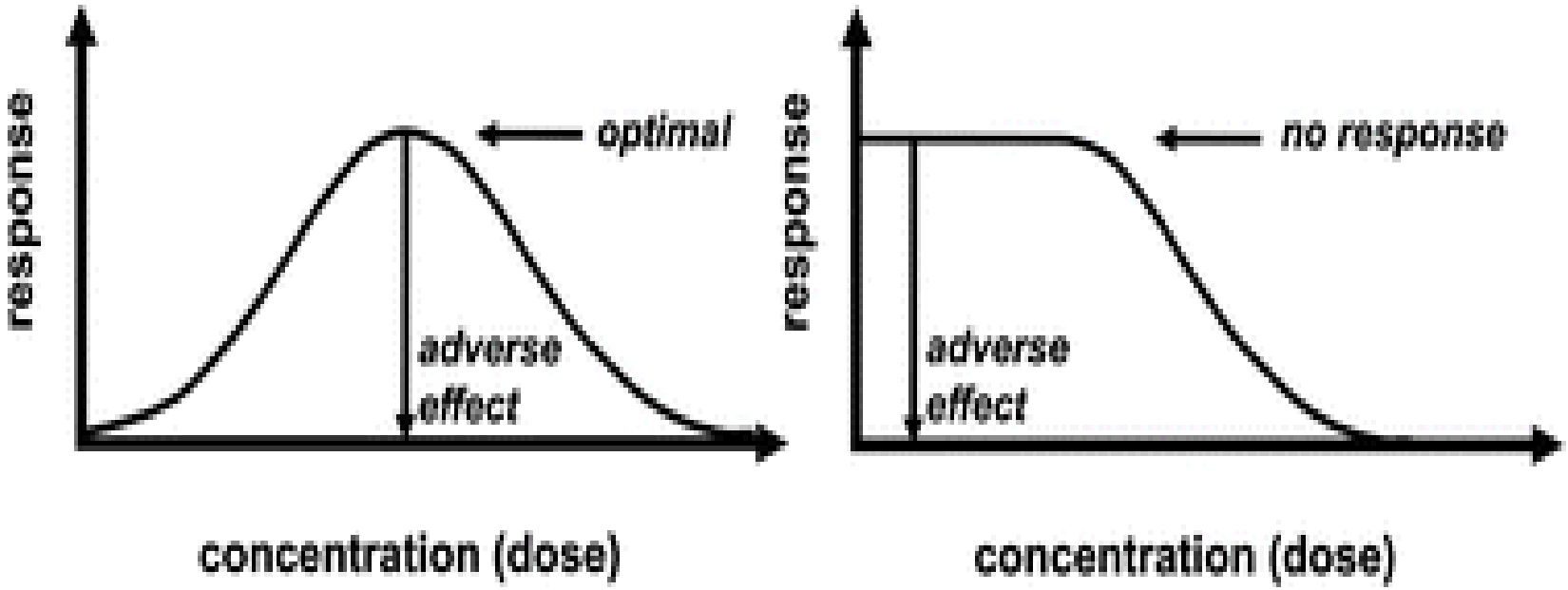
4.Repair or Disrepair



Dose – Response Curve for Toxicity

essential substance,
e.g. zinc

non-essential substance,
e.g. cadmium



Sodium

- **Hypernatremia-**It is a condition in which blood sodium level is high(more than 145 mEq/L).
- **Symptoms-**Thirst, brain cell shrinkage, confusion, muscle twitching, and in severe cases seizures and coma.
- **Treatment-** Administration of free water keeping electrolyte imbalance in mind.

Potassium

- **Hyperkalemia-**It is a condition of elevated blood potassium level.
- **Symptoms-**Malaise, palpitations, muscle weakness, levels higher than 5.5 mM have been associated with cardiovascular events.
- **Treatment-** Give insulin, salbutamol(shifts K^+ ions from blood stream to cellular compartment), Hemodialysis is required in severe cases(rapid method to remove it from the body)

Magnesium

- **Hypermagnesemia-**It is a condition in which Magnesium blood level is higher than 1.5 mM.
- **Symptoms**- Weakness, nausea, vomiting, impaired breathing, low blood pressure, low blood calcium, low heart rate, dizziness, decreased tendon reflexes.
- **Treatment-** Give calcium gluconate, give diuretics intravenously and when kidney function is impaired dialysis is done.

Zinc

- Zinc toxicity occurs after ingestion of more than 225mg of zinc. Excessive absorption of zinc can suppress copper and iron absorption.
- **Symptoms**- nausea, vomiting, pain, cramps, diarhhea, induced copper deficiency, alterations in blood lipoproteins level.

Calcium

- **Hypercalcaemia**-It is a condition of elevated Calcium blood level.
- **Symptoms**- stones(renal and biliary), bone pain, abdominal pain, nausea, vomiting, fatigue, anorexia, psychiatric overtones.
- **Treatment**-hydration, increased salt uptake, forced diuresis, in extreme cases drug could be given(plicamycin, gallium nitrate)

Copper

- **Copperiedus-**It is the consequence of excess copper in the body.
- **Symptoms**- Vomiting, hematemesis, hypotension, melena, coma, jaundice, gastrointestinal distress, damage to kidney and liver.
- **Treatment**- Drugs like penicillamine, dimercaprol, alpha-lipoic acid(ALA) could be used(chelation therapy)

Iron

- Iron levels above 350–500 µg/dL are considered toxic, and levels over 1000 µg/dL indicate severe iron poisoning.
- **Symptoms**-stomach pain, nausea, vomiting, metabolic acidosis, hypovolemic shock, damage to brain and liver.
- **Treatment**-using chelating agent like deferoxamine, if that doesn’t work dialysis.

The Bio-Inorganic Chemistry Of Quintessentially Toxic Metals

Arsenic

- Arsenic and its compounds are potent poisons.
- **Symptoms**-headache, confusion, diarrhea, hair loss, stomach pain, convulsions, vomiting blood, blood in urine

Arsenic poisoning is related with heart disease, cancer, stroke, diabetes, chronic lower respiratory diseases. It can eventually lead to multiple organ failure, coma and death.

Treatment- Chelation therapy using dimercaprol, dimercaptosuccinic acid, giving supplemental potassium, absorbents like activated carbon, aluminium oxide could be used, bacteria, yeast, fungi, and algae can also be used for remediation processes.

Mercury

- Mercury compounds produce toxicity and eventually death with less than a gram.
- **Symptoms**-Peripheral neuropathy, presenting as itching, burning, pain, formication, skin discoloration, swelling, desquamation, kidney dysfunction, emotional lability, memory impairment, or insomnia.

Children may have red cheeks, nose, and lips, loss of hair, nails and teeth, transient rashes, hypotonia, increased sensitivity to light

- **Treatment**-decontamination(remove clothes, wash skin with soap and water, flush the eyes with saline solution)

Chelation therapy using drugs like DMSA, 2,3-dimercapto-1-propanesulfonic acid (DMPS), D-penicillamine (DPCN), or dimercaprol (BAL).

Cadmium

- Cadmium overexposures may occur even in situations with trace quantities.
- **Symptoms**-cough, dryness and irritation of the nose and throat, headache, dizziness, weakness, fever, chills, and chest pain, respiratory and kidney failure. It causes Itai-Itai or Ouch-Ouch disease.
- **Treatment**-
  - Inhalation: fluid replacement, supplemental oxygen, mechanical ventilation.
  - Ingestion: gastric lavage

Lead

- The standard elevated blood lead level for adults is 10 µg/dl and for children it is 5 µg/dl.
- **Symptoms-** insomnia, delirium, cognitive deficits, tremor, hallucinations, convulsions, headache, abdominal pain, memory loss, kidney failure, male reproductive problems, and weakness, pain, or tingling in the extremities

Treatment-chelation therapy using edetate disodium calcium ($CaNa_2EDTA$), dimercaprol(BAL), which are injected and succimer and d-penicillamine, which are administered orally. Treatment of iron, calcium, and zinc deficiencies, which are associated with increased lead absorption, is another part of treatment for lead poisoning.