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Review Article

The essential metals for humans: a brief overview

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ABSTRACT

The human body needs about 20 essential elements in order to function properly and among them, for certain, 10 are metal elements, though for every metal we do need, there is another one in our body we could do without it. Until about 1950 poor attention was given to the so-called "inorganic elements" and while researches on "organic elements" (C, N, O and H) and organic compounds were given high priority, studies on essential inorganic elements were left aside.

Base on current knowledge it is ascertained today that metals such as Na, K, Mg, Ca, Fe, Mn, Co, Cu, Zn and Mo are essential elements for life and our body must have appropriate amounts of them.

Here a brief overview to highlight their importance and current knowledge about their essentiality.

1. Introduction

Although it is continuously discussed which elements should be classified as toxic, beneficial or essential for living organisms especially for humans, around 20 of the known elements are defined as essential today, though the precise requirements can differ within different organisms (Fig. 1).

First, there are the "organic" and "bulk" elements H, C, N, and O. In addition seven "macro-minerals" are essential, namely Na, K, Mg, Ca, Cl, P, and S.

Furthermore, "trace elements" are defined as essential, namely Mn, Fe, Cu, Zn, Se, Co, Mo and I for plants or animals. At present, some other elements are under discussion to be included in the category as essential for both, such as for example V, Ni, Br, Si, Sn [1–4].

For As, but also for Pb a positive effect of traces has been discussed for certain organisms, indicating the uncertainties in classification of many trace elements [5].

In fact, a dose-response diagram (Fig. 2) shows that also essential elements for human life can be toxic if the dose is high enough, pointing to the Paracelsus principle "the dose makes the poison".

Possibly, during the evolution of life, a biological function could be developed for all natural occurring elements. It is noteworthy that elements such as silicon or aluminium that are so abundant in the earth's crust play only marginal roles in the biological systems and this has been related to the water insolubility of their compounds, oxide or hydroxide, at physiological pH. On the other hand, a rare element such as for example molybdenum is quite soluble as MoO_4^{2-} oxyanion at physiological pH and it has been found to be essential in many living organisms [6].

2. Essential metal elements

Which elements are essential or beneficial and which are non-essential and only toxic for a certain organism is still under discussion, particularly for humans [7].

Despite the complexity of their functions, some characteristic deficiency symptoms of metal elements for humans are quite familiar and are reported in Table 1 [8].

As far as the toxicity is concerned, two groups can be distinguished: those for which the low abundance or the low bioavailability make them not necessary for life, and those elements for which only negative effects have been found so far. In this latter group metals with "Soft" acid chemical character are included, such as thallium, lead, mercury and cadmium [9].

The importance of a number of "inorganic elements", metal elements, as essential components of living organisms is well demonstrated, in particular for human beings.

The list of the metal elements that are today considered essential for

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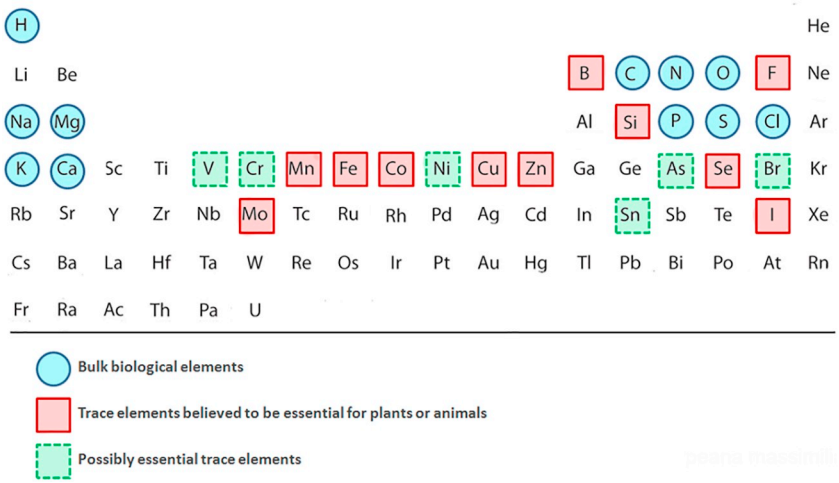

Fig. 1. The periodic table of the chemical elements required for life.

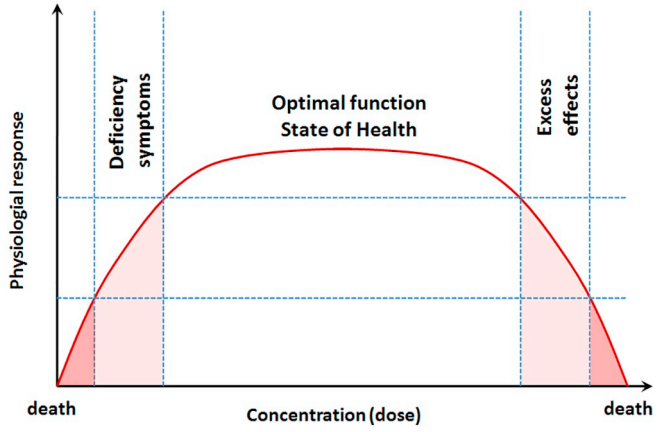

Fig. 2. Dose-response diagram for an essential element.

Table 1
Deficiency symptoms; *in some organisms. From reference [2].

Element	Deficiency symptoms
Ca	Retarded skeletal growth
Mg	Muscle cramps
Fe	Anemia, immune system disorders
Zn	Skin damage, stunted growth, retarded sexual maturation
Cu	Artery weakness, liver disorder, secondary anemia
Mn	Infertility, impaired skeletal growth
Mo	Retardation of cellular growth, propensity for caries
Co	Pernicious anemia
Ni	Growth depression, dermatitis*
Cr	Diabetes symptoms*

humans includes Na, K, Mg, Ca, Mn, Fe, Co, Cu, Zn, Mo, whereas some others such as V, Ni and Sn, are presumed but not ascertained to be essential for humans [10].

Regarding Cr, it was considered essential for humans until few years ago on the base of results with experimental animals. Animals which do not have chromium in their diet have been shown to get impaired ability to use glucose in the diet; the same should be true for humans, but more recent researches have excluded it from the list of essential elements [11,12]. Furthermore, Cr^{3+} may interfere with iron absorption. Thus, Cr^{3+} may be considered a pharmacological agent rather than an essential metal [13,14], though the issue is still under debate. On the other hand, Cr(VI) is considered toxic in that it may be involved in chromium induced cancer [15].

First of all, to be categorized as essential an element must satisfy the following conditions:

1. It must be present in the human tissues.
2. Its total absence in our organism causes irreversible and severe damage to the vital functions.
3. The reduction in physiological function can be normalized by appropriate supplementation of the element.

If one metal element is useful only to improve the organism functionality it should be better referred to as “beneficial” element and its dietary deficiency must result in a reduction of a biological function from optimal to suboptimal.

A non-negligible quantity of non-essential metals, such as Li, Rb, Sr, Zr, Pb, but also Au, U and some others, can nevertheless occur in our body. These elements are taken up from food, water, air, often because of their chemical similarity and character with important essential metals and their affinity for the same donor atoms and chemical sites of the essential metals. For example the “Hard” Sr^{2+} resembles Ca^{2+} and we can find it, in larger amounts than many essential metals, bound to phosphates in our bones. Although Sr^{2+} is not essential, it has been shown to protect against osteoporosis, and its ranelate salt has been classified as a beneficial drug [16]. Similarly, Li^+, Rb^+ or Cs^+ can substitute for Na^+, and Li^+ is also a well-known drug for the treatment of bipolar disorder [17–19]. Al^{3+} and Zr^{4+} can in some compounds substitute for Fe^{3+}, depending on their charge and size. Thus, uptake of an element by a biological system is not a proof of essentiality.

In Table 2 the 10 essential metal elements for human beings and their average amount in the adult reference man, average weigh 70 kg, is reported.

Table 2
Essential metal elements to the human body (body weight of Reference Man of 70 kg). From reference [7].

Element	Medium amount
Ca	1000 g
K	140 g
Na	100 g
Mg	30 g
Fe	5 g
Zn	2 g
Cu	100 mg
Mn	16 mg
Mo	5 mg
Co	2 mg

Table 3
Ligands and geometries preferred by different metal ions. From reference [2].

Metal ion	Coord. no	Geometry	Ligands
Na^+	6	Octahedral	O-donor, hydroxyl, carboxylate
K^+	6–8	Flexible	O-donor, hydroxyl, carboxylate
Mg^{2+}	6	Octahedral	O-donor, carboxylate, poly- and phosphate, N-donors
Ca^{2+}	6–8	Flexible	O-donor, carboxylate, carbonyl, phosphate,
Mn^{2+} (d^5)	6	Octahedral	O-donor, carboxylate, phosphate, Nitrogen-donor, imidazole
Mn^{3+} (d^4)	6	Tetragonal	O-donor, carboxylate, phosphate, hydoxime
Fe^{2+} (d^6)	4	Tetrahedral	S-donor, thiolate
	6	Octahedral	O-donor, carboxylate, alkoxide, oxide, phenolate, N-donor, imidazole, porphyrins
Fe^{3+} (d^5)	4	Tetrahedral	S-donor, thiolate
	6	Octahedral	O-donor, carboxylate, alkoxide, oxide, phenolate, Nitrogen-donor, imidazole, porphyrins
Co^{2+} (d^7)	4	Tetrahedral	S-donor, thiolate, N-donors, imidazole
	6	Octahedral	O-donor, Carboxylate, N-donors, imidazole
Cu^+ (d^{10})	4	Tetrahedral	S-donor, thiolate, N-donors, imidazole
Cu^{2+} (d^9)	4	Tetrahedral	S-donor, thiolate, N-donors, imidazole
	4	Square planar	O-donor, Carboxylate, N-donors, imidazole
	6	Tetragonal	O-donor, Carboxylate, N-donors, imidazole
Zn^{2+} (d^{10})	4	Tetrahedral	O-donor, Carboxylate, carbonyl, S-donor, thiolate, N-donors, imidazole
	5	Square pyramidal	O-donor, Carboxylate, carbonyl, N-donors, imidazole

As we can see, some closed shell metals are included: metals of the 1st and 2nd group and most of the 1st series of transition metals and one of the 2nd series of transition metals are also included. Considering that water is the solvent where they can act, essential metal elements can be found as cations, except for molybdate oxyanion.

On the other hand, virtually all the biological polymers: membranes, ribosomes, DNA, RNA, nuclei, lipids, etc. are negatively charged (carboxylates, phosphates, etc.). As a consequence there is an obvious need to neutralize the negative charges in the form of polyelectrolytes. Protons are not able to do that because the anions are strong acids and weak bases at physiological pH. However, Na^+, K^+, Mg^{2+} can well fulfill a neutralizing function, in vivo.

It is not surprising that elements as calcium heads the list - in fact it has be found in a quantity around 1000 g and 99% of the human's calcium constitutes along with phosphate the skeleton. Regarding the average elemental composition of a human body, calcium, the first metal element, ranks the fifth position among the essential elements in general, after the “organic elements” oxygen, carbon, hydrogen and nitrogen.

With regard to quantitative presence, potassium and sodium are the next two most present metals and operate among other functions to transmit to and from the brain the nervous impulses. Lower quantities are present of magnesium, iron and zinc, and dietary deficiencies are frequently reported. On the contrary, for example iron can also be present in excess, in the diet and in the body. Zn with about 2 g per 70 kg weight is the second most abundant among the transition metals in the human body.

The last metals on the list are present in very small quantities, “in traces”, but nonetheless they have important functions.

The first evidence is that the “chemistry of life” is mainly the chemistry of the lighter elements, which have atomic number lower than 36, except molybdenum (atomic number 42 and which can be classified both a metal or a non-metal depending on its oxidation state), including metal as well as non-metal elements. Besides, the essential elements have been selected from almost all groups of the periodic table, except the 3rd and 4th group of transition metals plus that of the noble gases. Scandium and titanium don't have any biological importance and the same applies to most other heavy metals mainly to the left of the periodic table whose compounds are almost insoluble at pH 7–7.4 such as for niobium, tantalum, zirconium, hafnium, or technetium, rhenium as well as the platinum metals which are often too rare to have biological relevance.

There is no a periodic chemical property of an element that makes it essential for human beings, but all kinds of periodic properties: dimension, oxidation states, periodic properties can be associated with life processes, except for the HSAB (Hard Soft Acid Base) chemical character [20,21].

Some general characteristics of metal complexes that can be found in biological systems are reported in Table 3. “Hard” and “Soft” character of essential metal ions is reported in Table 4 [22].

Looking at Table 4, some guidelines for cataloging metals for life can be derived.

In fact, the HSAB (Hard Soft Acid Base) theory is very useful in organizing the biology of metals.

The most important functions together with the preferred ligands and donor atoms for essential metals are reported in Table 5.

We can see that the “Soft” acids rarely are essential for life, and, on the contrary, they are often toxic (Hg^+, Hg^{2+}, Cd^{2+}, Tl^+). The HSAB principle predicts which ligands are preferred by a metal ion. “Soft” acids prefer “Soft” bases, then “Soft” metals, also in a very low concentration, are able to disrupt the structure and function of enzymes through the breaking of hydrogen bonds or S—S bonds by forming S-metal bonds.

Thus, important enzymes are deactivated by “Soft” metal ions. Then, most of the “Soft” metal ions are toxic if present in the body in amount of tenth of milligrams/kg of weight; no one of the typical “Soft” metal ion is essential, except Cu^+, which can be present during redox reactions involving Cu^{2+} ions or intracellularly tightly bound by specially designed chaperones and metalloenzymes.

Several “Hard” acids are essential for life (Na^+, K^+, Ca^{2+}) and because of their abundance are predestined for a non-catalytic function. Their binding to ligands is mostly weak and for their ionic mobility can be used to transfer information and as hydrated ions can selectively pass through membranes. This electric current can transmit nervous impulse. Mg^{2+} and Ca^{2+} have structural scopes: as phosphate or carbonate in bones, teethes, and stabilize anionic structures via electrostatic interactions.

Many of the “borderline” metal ions are essential also if they are present in “trace”. Their appreciable Lewis acidity make them able to specifically coordinate to some ligands (i.e. O_2) or to improve the acidity or reactivity of ligands.

Some “borderline” metal ions have several accessible oxidation states, sometimes differing only by one electron, which allow them to catalyze important redox reaction in enzymes.

Metal ions or their compounds have several biological functions which can then be summarized as follows:

- Participation in assembly hard structures via bio-mineralization: Ca^{2+} or Mg^{2+} participate to solid-state or structural functions. For example, the structure of double helix of DNA is maintained by the

Table 4
Hard and soft acids and bases. From reference [2].

Hard	Borderline	Soft
Acids H^+, Li^+, Na^+, K^+, Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Sc^{3+}, Al^{3+}, Ga^{3+}, In^{3+}, Cr^{3+}, Co^{3+}, Fe^{3+}, Ir^{3+}, La^{3+}, Si^{4+}, Ti^{4+}, Zr^{4+}, Th^{4+}, U^{4+}, VO^{2+}, UO_2^{2+}, $BeMe_2$, BF_3, BCl_3, $B(OR)_3$, $AlCl_3$, $AlMe_3$	Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Sn^{2+}, Pb^{2+}, Rh^{3+}, $B(CH_3)_3$, R_3C^+, SO_2, NO^+	Cu^+, Ag^+, Au^+, Hg^+, Cs^+, Tl^+, Hg^{2+}, Pd^{2+}, Cd^{2+}, Pt^{2+}, MoO_2^{2+}
Bases H_2O, OH^-, F^-, $CH_3CO_2^-$, PO_4^{3-}, SO_4^{2-}, CO_3^{2-}, NO_3^-, ClO_4^-, O^{2-}, ROH, RO^-, R_2O, NH_3, RNH_2, N_2H_4	Aniline, pyridine, N_3^-, Cl^-, Br^-, NO_2^-, SO_3^{2-}, N_2	S^{2-}, RSH, RS^-, R_2S, I^-, CN^-, SCN^-, $S_2O_3^-$, R_3P, R_3As, $(RO)_3P$, RNC, CO, C_2H_4, C_6H_6, R^-, H^-

presence of mono- or divalent cations, which significantly reduce the electrostatic repulsion forces between the nucleotide phosphate groups that are negatively charged.
- Very fast transfer of information by charge carriers (Na^+, K^+)
- Participation in degradation, formation or metabolism of organic compounds by metal sites in several enzymes (Zn^{2+}, Mg^{2+})
- Transfer of electrons in redox pairs, also by stabilizing “unusual” oxidation states of redox-active metals: Fe(II), Fe(III), Fe(IV); Cu(I), Cu(II); Mn(II), Mn(III), Mn(IV); Mo(IV), (V), (VI); Co(I), Co(II), Co (III)
- Carrying out difficult reactions under physiological conditions: most of the transition metals are able to both provide unpaired electrons and to concurrently donate electronic charge through a π back donation bonding.

3. Biological relevance of essential metal elements

Metal elements can be taken up, accumulated, transported or stored depending on their function and activities.

Though there is a long pathway to be undertaken before our understanding of the complex biological chemistry of life, some of the most important biological functions of essential metal elements are summarized here [2,3,23].

3.1. Calcium

This is the most abundant inorganic constituent of the human body, accounting for about 1 kg of the body weight. The ideal calcium intake is around 700–800 mg a day; cheese, milk can provide about 200 mg per 100 g and in order to utilize calcium in the diet vitamin D is needed [24].

Table 5
The most important functions together with the preferred ligands and donor atoms for essential metals. From reference [3].

Metal ion	Function	Binding group and donor atoms
Hard acid		
Na^+	Charged ion	Hydrated ions, (O)
K^+	Charged ion	O-donor, charged −1 or neutral (O)
Mg^{2+}	Charged ion, structural	O-donor, carboxylate, poly- and phosphate, N-donors
Ca^{2+}	Charged ion, structural	As Mg^{2+} but with minor affinity for N-donors, phosphate and other multi-dentate anions
Fe^{3+}	Redox reactions	Carboxylate (O), tyrosine (O), -NH_2 (N), porfirine (“hard” N)
Co^{3+}	Redox reactions	Like Fe^{3+}
Borderline acid		
Mn^{2+}	Lewis acid	Like Mg^{2+}
Fe^{2+}	Redox reactions	−SH (S), $-NH_2$ (N) > carboxylate (O)
Zn^{2+}	Lewis acid	Imidazole (N), cysteine (S)
Cu^{2+}	Redox reactions	Amine (N) ≫ carboxylate (O)
Mo^{2+}	Redox reactions	−SH (S)
Soft acid		
Cu^{2+}	Lewis acid	Cysteine (S)

As hydroxyapatite, $Ca_5(PO_4)_3(OH)_2$, calcium is a major component of normal bone and teeth. Hydroxyapatite makes up the bone mineral and the matrix of teeth, and this calcium compound gives bones and teeth their rigidity. Calcium is a cofactor for numerous enzymes and is also important for intracellular functions as a messenger in cascade signaling reactions, for example, muscle and nerve function and impulses, cell division and for blood coagulation, keeping blood pH stable. The blood plasma levels of total calcium are kept fairly constant, within narrow limits, 2.2–2.6 mmol/L (9–10.5 mg/dL). However, about 50% of this blood plasma calcium is bound to albumin, and measurements of “ionized” calcium (1.1–1.4 mmol/L or 4.5–5.6 mg/dL) may be the recommended analysis, since the amount of total calcium varies with the level of albumin. If the diet provides insufficient amounts of this element, the organism will mobilize calcium from bone, through a process that is brought about by increased circulating levels of the parathyroid hormone (PTH). Bones are able to keep the level of calcium in the blood stable in order to cover all the functions of this metal ion [25,26].

Hypercalcemia disorder affects the neuromuscular, gastrointestinal, renal, skeletal, and cardiovascular systems. The most common causes of hypercalcemia are primary hyperparathyroidism and malignancy. Some other important causes of hypercalcemia include overdoses of vitamin D. Hypercalcemic crisis with total Ca above 14 mg/dL (or above 3.5 mmol/L) is a life-threatening emergency, often precipitated by malignancy. Aggressive intravenous rehydration is the mainstay of management in severe hypercalcemia, and an intravenously administered bisphosphonate (pamidronate or zoledronate) can usually alleviate the clinical manifestations of hypercalcemic disorders. Whereas bisphosphonates have Ca-chelating properties, the previous use of another chelator, disodium-EDTA, in hypercalcemia is considered obsolete today. In hypercalcemia mediated by vitamin D and in hematologic malignancies, for example myeloma, glucocorticoids may be the first line of therapy after fluids [27,28].

Hypocalcemia may occur due to hypoparathyroidism, acute or chronic kidney failure, low vitamin D intake, genetic anomalies, or iatrogenic causes related to some antiosteoporosis or chelation drugs. In chronic hypocalcemia bone mineralization may be compromised, whereas acute cases may present by convulsions, tetany, or numbness [29].

3.2. Potassium

The adult human body contains about 140 g of potassium. The daily intake should be about 3.5 g a day and almost all food contains potassium; the most rich are nuts and seeds which may contain up to 1%, yeast extract or coffee between 3 and 4% by weight of this essential metal [24].

All part of human body can contain potassium. This cation occurs predominantly intracellularly and contributes significantly to the intracellular osmolality and its most important role is the activity in nervous system [30]. Blood plasma potassium levels are normally kept within a narrow range of 3.5 to 5.0 mmol/L, whereas intracellular levels are significantly higher. Potassium content in the plasma is tightly

controlled by several mechanisms. Renal excretion represents one of these mechanisms. A mechanism of particular importance is the so-called ion transport system, usually referred to as the sodium/potassium-ATPase pump. This pump moves potassium across the cell membrane into the cell, while sodium is pumped out of the cell. In this way, potassium and sodium cations influence fluid distribution between intracellular and extracellular compartments by osmotic forces. Movement of potassium and sodium across the cell membrane is basically mediated by this sodium/potassium pump, which uses ATP to translocate sodium ions out of the cell and at the same time potassium ions into the cell, creating an electrochemical gradient across the cell membrane [30]. The electrochemical potential in nerves depends on the physiological presence of potassium intracellularly. An adequate potassium/sodium balance across the membrane is of importance for the signaling in nerves. In the intracardial pathways of signaling and regulation of heart rhythm, potassium is of particular significance. Some other elements such as lithium, cesium, and thallium have chemical similarities with potassium, and may displace potassium from important intracellular locations.

Hyperkalemia is defined as plasma potassium levels above 5.5 mmol/L. In severe cases this can results in cardiac arrhythmias with palpitations, in addition to a generalized muscle weakness. If severe abnormalities in heart rate occur, hyperkalemia can result in cardiac arrest and death. This may happen in severely affected cases with plasma values above 6.5 mmol/L. Such high levels can also be detected on an ECG (electrocardiography). The most common cause of hyperkalemia is related to acute or chronic kidney disease. Other causes include adrenal insufficiency (Addison's disease) or long-term use of angiotensin-converting enzyme (ACE) inhibitors. Initial treatment in patients with ECG changes is calcium gluconate. Any drug that might worsen the condition should be stopped. In addition some cases may need treatment with glucose and insulin. Hemodialysis is the most effective method in severe cases [31].

Hypokalemia refers to a state of deficiency of potassium in the plasma, which can be fatal if severe. Common causes are increased gastrointestinal losses due to vomiting or diarrhea, or increased renal losses often due to long-term use of diuretics. Inadequate potassium intake is a rare cause of hypokalemia [32]. Disease states leading to abnormally high aldosterone levels (hyperaldosteronism) can cause excessive urinary losses of potassium. Deficiency symptoms include muscle weakness, ECG abnormalities, decreased reflex response; and in severe cases, cardiac arrhythmias. Mild hypokalemia (> 3.0 mmol/L) may be treated orally with potassium chloride tablets. Potassium-containing foods may also be recommended. Severe hypokalemia (< 3.0 mmol/L) may require intravenous treatment, typically using a physiological saline solution supplemented with about 30 mmol KCl per liter given over up to 4 h.

3.3. Sodium

Ordinarily, the adult human body contains about 100 g of sodium. The medium daily intake is around 3 g and a regular supply is needed because it is lost by the kidney from the blood stream. Unphysiologically high intakes of sodium as table salt may increase the blood pressure. A general recommendation based on an overall evaluation of available data states that Na intake in adults should not exceed 2.4 g/day, which corresponds to a limit of about 6 g/day of table salt (NaCl) [33].

Sodium is the extracellular counterpart of potassium. It regulates the amount of water in the extracellular space via osmotic homeostatic processes together with other electrolytes and macromolecules, and together with potassium it regulates the total amount of water in the body. In nerves sodium is fundamental for the electrical signaling [30].

Blood plasma sodium levels of sodium are normally kept within a narrow range of 135–145 mmol/L, whereas the intracellular levels are low.

Hypernatremia is a state with high concentrations of sodium in blood plasma, exceeding the physiological upper level of 145 mmol/L [34,35]. Early symptoms may include a strong feeling of thirst combined with weakness and nausea. Severe symptoms typically occur when levels exceed 160 mmol/L and may include mental confusion, muscle dysfunctions and in the most severe cases intracerebral spot bleedings. Loss of water due to renal disease may precipitate hypernatremia. Among other conditions that can lead to increased blood sodium levels are hormonal disorders including diabetes insipidus and hyperaldosteronism. Too much intake of salt is a rare cause of hypernatremia. In general, it is recommended that therapeutic correction should occur rather slowly, in mild cases by drinking of water.

Hyponatremia is generally defined as plasma sodium concentrations < 135 mmol /L while *severe* hyponatremia denotes a state with values below 120 mmol/L [36]. Mild symptom of hyponatremia may include unspecific dizziness and headache, whereas severe hyponatremia may give rise to alarming neurological symptoms involving lethargy, severe confusion, seizures and coma. As far as therapy is concerned, it is important to eliminate the cause of the hyponatremia and to carry out a controlled correction with isotonic or hypertonic saline. Too rapid correction can precipitate a serious cerebral complication called osmotic demyelination syndrome.

3.4. Magnesium

Among the cations in the human body, magnesium is the fourth in abundance, and it is the second intracellular cation in tissues [37]. The human body contains about 30 g of magnesium, 50% stored in bones, and the remaining in body fluids, soft tissues, and muscles. Although only 1% of the total magnesium is found in blood, the concentration of magnesium in serum (SMC) is the main medical test used to assess the magnesium status in patients [38]. Magnesium plays a vital role in more than 300 enzymatic reactions, among which the transmission of nerve impulses and the synthesis of fatty acids and proteins. Magnesium plays a fundamental role in biology: ATP needs to be bound to a magnesium ion to be biologically active and in formation of the transition state where ATP is synthesized from ADP and inorganic phosphate [39]. Magnesium released from the breakdown of bones is a vital cofactor essential for multiple metabolic enzymes that are up regulated in activated immune cells. Consequently, the human content of magnesium ions is a determining factor of the immune system [40]. Magnesium is also important in the structure of skeleton and muscles. The bones act as a magnesium store. The necessary magnesium intake in humans is evaluated in at least 100 mg per day [41]. Almonds, cocoa, brewer's yeast have more than about 200 mg of magnesium per 100 g [24].

3.5. Iron

About 5 g of iron can be found and it is the most abundant d-metal ion in the human body. A daily intake is around 7 mg and foods rich in iron are liver, beef, red wines, eggs though only a fraction can be absorbed, about as little as 25% [24].

Human genome codes for more than 500 iron proteins. Iron is an essential element for practically all living systems.

It is implied in at least hundred enzymatic reactions: oxygen transport and utilization, DNA synthesis, electron transport, and Fe^{2+} represents the oxygen-carrying core of hemoglobin [42].

About 80% of the total iron content is found in circulating red blood cells (hemoglobin) and in the muscle (myoglobin). The remaining 20% is distributed between the storage proteins ferritin and hemosiderin, a few hundred milligrams are involved in enzymatic processes, and about 3–4 mg circulate in the plasma bound to transferrin. Iron in plasma is turned over about 10 times a day. The metabolism of iron is basically conservative, with an average absorption of 1–3 mg/day, and an almost equal amount excreted by cell desquamation. In women it plays an

important role. The delicate equilibria between iron uptake and iron loss, and the mechanisms regulating iron uptake were accurately discussed by Crichton and Ward [43]. The extracellular amounts of the toxic "ionized iron" are negligible, since the plasma protein transferrin has extremely high affinity for Fe^{3+}. Extracellular hemoglobin may also act as a pro-oxidant, but intracellularly it is shielded not only by the red cell membrane, but also by intracellular glutathione (about 3 mmol/L) and the antioxidative enzyme glutathione peroxidase. In sickle cell anemia, thalassemia, and/or transfusional siderosis, toxic amounts of iron are deposited in liver, heart, and other organs.

In its inorganic compounds it presents various oxidation states: 0, +2, +3, +4 and +6. The rich and varied coordination chemistry is the main reason for the unusual suitability of iron in all the biological system. In both of the two common oxidation states Fe^{3+} and Fe^{2+}, it is able to adopt different coordination environments with full or empty coordination sites. The redox potential Fe^{3+}/Fe^{2+} can be modulated by the properties of the coordinated atoms. The chemical features render this metal appropriate for the transport and activation of small molecules and for the electron transfer processes. The ionic radius of 67 pm and the positive charge +3 mark free Fe^{3+} as a "hard" acid, which prefers "hard" oxygen ligands. On the contrary, free Fe^{2+}, with an ionic radius of 83 pm and a positive charge +2, is borderline between "hard" and "soft" acid character, and its coordination by nitrogen atoms is favored compared to oxygen ligands [44].

Iron can be toxic when present in excess. In the presence of molecular oxygen, loosely bound iron is able to redox cycle Fe^{3+}/Fe^{2+} generating poisonous oxygen-derived free radicals (ROS). The cells adopt a number of protective strategies to avoid such event, including iron storage and tightly controlled iron transport.

Recently, relations between Fe deficiency and overloading was considered [45]. $Fe(SO_4)_2$ was largely used as an oral supplement as far back as 1832. It is also reported that iron bioavailability is dependent by plant foods, comprising polyphenols and tannins [46].

3.6. Zinc

The average 70 kg human contains Zn in about 2 g amount, being the most abundant essential d-metal ion, following iron. High concentration of Zn can be found in vesicles in the brain, in bones and muscles [47]. It is reported that a recommended dose is around 15 mg/day [48] and that low cellular Zn amount can induce stunted growth and development and apoptosis in several cells [49,50].

Zinc deficiency in developing countries leads to decreased resistance against infection, particularly in children, and in severe cases, it may lead to hypogonadism and dwarfism [51,52].

Abundant intakes of zinc induce synthesis of a metal-binding protein, metallothionein, also in gut mucosal cells, and may thereby protect against toxic actions of copper, for example, in Wilson's disease [53]. Zn^{2+} is a ubiquitous ion which can play several roles such as structural, catalytic, regulatory [49].

It takes part in the enzymatic action of more than 300 proteins: carbonic anhydrase, superoxide dismutase, alkaline phosphatase, for an example [54,55].

It is found in association with RNA polymerases with the catalytic role in the acid-base reactions. It has important functions in organizing the tertiary structure of proteins via zinc fingers. Many zinc finger proteins function *via* interactions with nucleic acids, for example, regulation of gene expression by transcription factors interacting with DNA responsive elements through zinc fingers.

Zn^{2+} ion can be considered as a major regulatory ion among the redox inert metal ions Na^+, K^+, Mg^{2+}, Ca^{2+}, sharing with calcium the signaling capacity. Zn^{2+} ions are able to behave as messengers of intracellular information as well as input of extracellular communication; thus they have a role in the transmission of information inside the cells as well as in communication among the cells. The Zn regulatory pathway interacts with Ca^{2+} ions signaling [56–58]. The reason for Zn in Lewis-acid function and not Fe can be that Zn is a better Lewis acid and it does not function as a redox catalyst and then it is not able to damage DNA [1].

3.7. Copper

About 100 mg of it is present in our body and among the essential d-metals is the third most abundant [59]. The daily intake of Cu is around few mgs.

Several foods are rich in this essential metal: meats, where it is present as a copper protein, kidney and liver, oyster, lobster, mushrooms, nuts, almonds [60], therefore dietary intake of copper ions can generally exceeds tissue requests, so homeostatic mechanisms are able to regulate both uptake and export in order to maintain a sufficient supply while minimizing toxic properties.

It is important in various enzymatic reactions, particularly as an electron donor and for enzymes that are important to our ability to use oxygen actively. In the respiratory chain in mitochondria, the copper enzyme cytochrome *c* oxidase operates as an electron transporter [61,62]. Cytochrome c oxidase is one of the most important protein with three copper centers per monomeric protein complex [2,63].

Copper participates also in the formation of connective tissue, as collagen and keratine.

Cu^{2+} ions are carried out inside the cells through specific copper transporter and reduced to Cu^{+1} ions. Again specific copper metallochaperons assist it in reaching specific target enzymes without causing damage or becoming trapped in several binding molecules [64].

Free copper ions are found in living organisms in a very low concentration to prevent the possibility of inducing highly reactive free radicals through the Fenton reaction, during cycling between the two common +1 and +2 oxidation state in several copper enzymes [65].

Though copper is essential, it can be toxic in a high quantity also because it is able to replace less competitive metal ions from metalloproteins, as zinc and iron, from their site of action. High intakes of copper may lead to several toxic effects as well as copper deficiency which can have severe outcomes frequently related to neurodegeneration.

In fact, several disorders can be associated to copper deviations:

- A syndrome connected to a hereditary dysfunction of the intracellular transport of copper: Menke's kinky hair accompanied by mental and physical growth disorders [66]
- An insufficient oxygen utilization in the brain and the permanent damage caused by acute deficiency of copper [67]
- Wilson's disease which induces copper overload in the brain and liver, leading dementia, liver injury and then death [68].

Mn, Mo, and Co found in the human body in concentrations ranging from 12 to 3 mg, may be needed in amount very low that a life's time supply could be no more than 30 g. They are essential for life because they are present in enzymes which catalyze important processes for human life (Co in B12, rearrangements, reduction; Mn, acid phosphatase; Mo, nitrate reductase, etc.).

3.8. Manganese

The average 70 kg human contains Mn in about 12–20 mg amount.

It is an essential metal for intracellular activities. It is a cofactor in a number of enzymes with functions in metabolism, regulation of cellular energy, reproduction, in the growth of bone and connective tissue, as Manganese superoxide dismutase, glutamine synthetase, arginase. Manganese superoxide dismutase (MnSOD) is of particular importance, since it protects mitochondria from toxic oxidants. The most abundant Mn enzyme in the body is glutamine synthetase which has an important role in the brain function [69,70].

There is any need for humans to take manganese supplements because usually we take it enough from our diet. Foods rich in manganese are almonds, blueberries, olives, avocados, rice, oats and tea. The daily dietary intake is from 1 to 10 mg that is not far from the 20 mg which is considered a dangerous intake.

In fact overexposure to manganese, for example exposure at the work place, may give rise to several outcomes. Manganese accumulates in the bones, liver, pancreas and mainly in the brain. Several pathologies, as polycythemia, dystonia, hepatic cirrhosis, have been related to its overexposure. In particular, symptoms as in Parkinsonism [71–73], the so-called "manganism", has been reported following manganese excess. The molecular mechanisms involved include oxidative stress, misfolding of protein, apoptosis, mitochondrial dysfunctions, and interference in the homeostasis of other metal essential ions.

The toxicity of Mn depends from its chemical form. Mn^{2+}, which is the normal form which takes it in is not dangerous; on the contrary MnO_4^- is considered very toxic, and exposure to dusts or fumes is considered a health hazard and the Mn amount should not exceed 5 mg/m^3, even for short periods.

Among the oxidation states, Mn(II), Mn(III) and Mn(IV) are the most important in biological system. Mn(II) has chemical similarity to Mg(II), although the activity of manganese is mainly related to its redox activity.

Several studies have been devoted to understand the mechanisms by which Mn ions enter the blood brain barrier: facilitated diffusion [74], as well as active transport [75] have been suggested. It is possible that several transporter molecules can be mutually responsible to maintain the optimal level of manganese ions in tissues [76].

Furthermore it has been reported that Mn transport in the brain and peripheral tissues can be mediated by iron transporters [77].

3.9. Molybdenum

The average adult person has about 5 mg of molybdenum, though this amount in a single dose would be dangerous. Liver, kidney, small intestine [78,79] contain the most of molybdenum. It is known that it is taken up by cells in the only form of $[MoO_4]^{2-}$ molybdate oxyanion, where Mo is in the (VI) oxidation state. The average amount intake for humans is around 0.3 mg a day. It is the only essential d-metal of the second and third series of the periodic table.

Foods that have the most molybdenum are lamb, beef liver, pork, lentils, peas. Despite the toxicity of this metal, molybdenum is essential to all species and molybdenum enzymes are ubiquitous, contrary to tungsten the heavier homologue metal element in the same group. This difference has been related to the lower reduction potential of tungsten compared to that of molybdenum centers [80,81].

Four molybdenum enzymes, belonging to the family of sulfite oxidase and xantine oxidoreductase, are coded from the human genome [82,83].

The xanthine oxidase mammalian enzyme is important for the production of uric acid to excrete unwanted nitrogen compounds from our body. Aldehyde oxidase that requires molybdenum is necessary in the metabolism of alcohol. Japanese people, which normally have low level of this enzyme, can metabolize alcohol much more slowly than other people [24].

Molybdopterin, a phosphorylated pyranopterin moiety [84] is the enzyme cofactor where Mo is bound to the enzymes active site [85]. Excluding nitrogenase, it is part of the active site of all the molybdenum enzymes [82]. Neurodegeneration and childhood death can be triggered by Molybdopterin deficiency caused by genetic diseases [78,86].

A role in medicine has been proposed in the treatment of diabetic mellitus for $[MoO_4]^{2-}$ ion [87], from the evidence that it is able to prevent lipids oxidation and protect antioxidant systems in experimental diabetic rats. In addition, $[MoS_4]^{2-}$ ion is in the phase II of clinical trials in the cure of esophageal and breast cancer [88].

Metabolism of Mo has been related to Cu metabolism following the identification of copper bound to the molibdopterin structure [85].

3.10. Cobalt

Though cobalt plays a vital role, only about 2 mg of it are in human body. It is essential as a component, the heart, of vitamin B12 (cobalamin) molecule, that is fundamental for several biological processes, especially for the transfer of methyl groups, for example, into DNA. The amount of cobalt we need is very small. The average recommended amount intake for humans is around few μg a day. Foods that contain it are sardines, salmon, peanuts, butter, molasses.

Whereas iron can be introduced into the resembling porphyrin ring in the human body by an enzyme iron chelatase, the entire cobalamin molecule must be supplied by the diet.

In the digestive tract, specific proteins are able to selectively absorb vitamin B12 from the diet and carrier proteins partecipate to the distribution of the vitamin [89,90].

The vitamin is normally bound to the gastric factor. A specific receptor complex that is formed by two proteins, amnionless and cubilin, included the vitamin in the ileum [91].

Pernicious anaemia can be a consequence of a deficiency. In this case the inactivation of methionine synthase or methylmalonyl-CoA mutase enzymes for which this cobalt vitamin is the necessary coenzyme, occurs [92].

An altered trafficking of the vitamin leads to a deficiency of it with consequent neurological and hematological pathologies [93].

A role in medicine for a cobalt complex has been found; Co(2-methylimidazole)$_2$ acacen complex has been tested against ophthalmic herpetic keratitis and adenovirus kerato conjunctivitis for which clinical phase I trial and against herpes labialis for which clinical phase II trial has been concluded [94].

3.11. Tin

Among the possible essential elements, the average person has about 20 mg of tin; there is more tin in the human body than it seems we should need. The daily intake for humans is around 0.3 mg. It results essential for several living organisms for which a tin free diet resulted in a not properly growth. This fact supports its essentiality for humans [1,95].

4. Toxic effects of essential and non-essential elements

Both essential and nonessential metals may exert toxic effects if the dose of ingestion or exposure exceeds certain levels [96], often referred to as *critical levels*. The effects induced at these levels by a toxic agent may be referred to as critical effects. These effects arises from the so-called *critical organ* [97]. For example, the central nervous system is the critical organ in cases of elemental mercury vapor exposure. When discussing metal toxicity it should be emphasized that not only concentration range, but also speciation and oxidation state are crucial factors that affect the poisoning aspects of the metal in question.

Dose-effect and dose-response relationships are fundamental concepts in toxicology. A dose-effect relationship exists if an increase in the dose of a chemical compound (here. of a metal ion, or of a metal compound) causes a quantifiable increase in the toxic effect observed or the occurrence of additional undesirable effects. On the other hand, if an observed effect is not quantifiable in single individuals, but is either present or not present (often called all-or-none effect), a *dose-response* relationship exists if the percentage of a population responding with that effect depends on the dose of the chemical. It is also possible to depict a quantifiable effect on a dose-response curve, by illustrating the percentage of the population with the value of a biomarker above a certain level, for example, beta-2-microglobulin in urine above a certain threshold.

The goal of chemical toxicity testing, and of toxicological research is

to identify potential adverse health effects that can be caused by low doses of unintentional exposure to environmental toxicants, for example, toxic metal ions or metal compounds.

One basic principle of the framework provided by National Research Council in the analysis of the dose-response curve is to define a window of interest in the lower part of the curve [98]. Reference dose (RfD): description and use in health risk assessments. *Regulatory toxicology and pharmacology*, *8*(4), 471–486.). This is the window between the lowest observed adverse effect level (LOAEL) and the no observed adverse effect level (NOAEL). Thus, the LOAEL is the lowest dose tested with a statistically significant effect, whereas the NOAEL is identified as the highest dose tested without a statistically significant effect.

The LOAEL identifies the more frequently used term “critical dose.” A more frequently used approach nowadays is to model the dose-response relationship with confidence limits [99].

However, the identification of a critical exposure, that is, a *benchmark dose* or LOAEL in an individual does not by itself constitute an indication for institution of chelation therapy.

Thus, in the case of lead, for instance in an analysis of several epidemiological studies, The European Food Safety Authority (EFSA) identified a BMDL01 (1% change, benchmark response) for neurocognitive effect in children of 12 μg/L in blood [100] whereas the US Centers for Disease Control and Prevention (CDC) use a reference value of 50 μg/L (0.24 μmol/L) in blood. This reference value is based on the 97.5 percentile of the National Health and Nutrition Examination Survey (NHANES) blood lead distribution in children. The present guidelines [101] involve that monitoring and removal of environmental lead is the action of choice at blood Pb levels in the range 50–450 μg/L (0.24–2.2 μmol/L), whereas chelation treatment is indicated only if blood Pb levels exceed 450 μg/L (2.2 μmol/L). In these cases, chelation with DMSA (Succimer) is recommended.

5. Conclusions

Here we have briefly reviewed metals which are today considered essential for human life, with no intention to present a comprehensive review, but rather an attempt to highlight current general knowledge about essential metal elements.

According to current knowledge, 60 of the elements in the Periodic Table are elements contained in human body but only about 20 of these are considered to be essential for life, no matter what type of organism is under debate, and to take part in the healthy functioning of human body, including one from most of the groups of the first three rows of the Periodic Table; among them 10 are metal elements absolutely human body must have.

Even though only few metal elements are essential for human life, a role in medicine as therapeutic agents for several other metals have been found [102–104]. Regarding some elements, such as Ni, Cr and V, their essentiality is still in contention. Presumably better analytical methods and more specific tests for “trace” elements have to be carried out before additional elements could be added. Though there is still a long way to go before we understand the biological chemistry of life, some of the biological functions of essential metal elements are reviewed from a chemical point of view. For example, for Zn^{2+} that doesn't act as a redox catalyst but it is the most stable Lewis acid available in biology, presumably explaining the presence of Zn^{2+} in more than 200 of enzymes; Na^{+} and K^{+}, with their particular properties together with their inability to bind tightly, are abundant in all the universe and required for all life.

Among the chemical properties of an element that makes it essential, none of particular periodic properties (dimension, oxidation number, electronegativity or others) can be considered essential for life. Indeed, essential elements have been selected from each group of Periodic Table, except the group 3 and 4 and the noble gases. A possible clue in classifying an element as an essential one or not, is the HSAB classification into Soft-Hard-acid-base chemical characteristics. As discussed, these characteristics can give an indication about the sites where the metal could exert its peculiar property and then its essentiality - or not. What is clear is that the integrated approach of biological and chemical sciences, metallomics, is necessary to understand the biology of bulk or trace metal ions, their interactions and speciation in the cellular compartments and human body, their biological functions correlated to their chemical properties.

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References

[1] R.J.P. Williams, The chemical elements of life, J. Chem. Soc. Dalton Trans. (1991) 539–546 (S).
[2] W. Kaim, B. Schwederski (Ed.), Bioinorganic Chemistry : Inorganic Elements in the Chemistry of Life: An Introduction and Guide, Wiley, Chichester, 1994.
[3] J.F. Da Silva, R.J.P. Williams, The Biological Chemistry of the Elements: The Inorganic Chemistry of Life, Oxford University Press, 2001.
[4] W. Mertz, The essential trace elements, Science 213 (4514) (1981) 1332–1338.
[5] F.H. Nielsen, Nutritional requirements for boron, silicon, vanadium, nickel, and arsenic: current knowledge and speculation, FASEB J. 5 (12) (1991) 2661–2667.
[6] P.A. Cox, The Elements. Their Origin, Abundance, and Distribution, Oxford University Press, Oxford (UK), 1989.
[7] W. Maret, The metals in the biological periodic system of the elements: concepts and conjectures, Int. J. Mol. Sci. 17 (1) (2016).
[8] A. Sigel, H. Sigel, R.K. Sigel, Interrelations between Essential Metal Ions and Human Diseases, Springer, 2013.
[9] A.T. Jan, M. Azam, K. Siddiqui, A. Ali, I. Choi, Q.M. Haq, Heavy metals and human health: mechanistic insight into toxicity and counter defense system of antioxidants, Int. J. Mol. Sci. 16 (12) (2015) 29592–29630.
[10] C. Horovitz, Is the major part of the periodic system really inessential for life? J. Trace Elem. Electrolytes Health Dis. 2 (3) (1988) 135.
[11] J.B. Vincent, New evidence against chromium as an essential trace element, J. Nutr. 147 (12) (2017) 2212–2219.
[12] K.R. Di Bona, S. Love, N.R. Rhodes, D. McAdory, S.H. Sinha, N. Kern, J. Kent, J. Strickland, A. Wilson, J. Beaird, J. Ramage, J.F. Rasco, J.B. Vincent, Chromium is not an essential trace element for mammals: effects of a “low-chromium” diet, JBIC Journal of Biological Inorganic Chemistry 16 (3) (2011) 381–390.
[13] D.M. Stearns, Is chromium a trace essential metal? BioFactors 11 (3) (2000) 149–162.
[14] J.B. Vincent, Is chromium pharmacologically relevant? J. Trace Elem. Med. Biol. 28 (4) (2014) 397–405.
[15] H. Sun, J. Brocato, M. Costa, Oral chromium exposure and toxicity, Curr Environ Health Rep 2 (3) (2015) 295–303.
[16] P. Costanzo, H. Salerni, A. Sánchez, Effect of strontium ranelate on bone mineral density in men with osteoporosis, Actualizaciones en Osteología 13 (3) (2017) 198–206.
[17] G.S. Malhi, M. Tanious, P. Das, C.M. Coulston, M. Berk, Potential mechanisms of action of lithium in bipolar disorder. Current understanding, CNS Drugs 27 (2) (2013) 135–153.
[18] C.T. Chiu, Z. Wang, J.G. Hunsberger, D.M. Chuang, Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder, Pharmacol. Rev. 65 (1) (2013) 105–142.
[19] A. Cipriani, K. Hawton, S. Stockton, J.R. Geddes, Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis, BMJ 346 (2013) f3646.
[20] R.G. Pearson, Hard and Soft Acids and Bases, Dowden, Stroudsburg (Pa.), 1973.
[21] M.N. Hughes, The Inorganic Chemistry of Biological Processes, 2nd edn, Wiley, 1981 Vol..
[22] R.G. Pearson, Hard and soft acids and bases, J. Am. Chem. Soc. 85 (22) (1963) 3533–3539.
[23] B. Lakatos, K. Szentmihalyi, P. Vinkler, J. Balla, G. Balla, The role of essential metal ions in the human organism and their oral supplementation to the human body in deficiency states, Orv. Hetil. 145 (25) (2004) 1315–1319.
[24] J. Emsley, Nature's Building Blocks: An AZ Guide to the Elements, Oxford University Press, 2011.
[25] C. Toyoshima, M. Nakasako, H. Nomura, H. Ogawa, Crystal structure of the calcium pump of sarcoplasmic reticulum at 2.6 A resolution, Nature 405 (6787) (2000) 647–655.
[26] M. Brini, T. Cali, D. Ottolini, E. Carafoli, The plasma membrane calcium pump in health and disease, FEBS J. 280 (21) (2013) 5385–5397.
[27] H. Sternlicht, I.G. Glezerman, Hypercalcemia of malignancy and new treatment options, Ther. Clin. Risk Manag. 11 (2015) 1779–1788.
[28] A.E. Mirrakhimov, Hypercalcemia of malignancy: an update on pathogenesis and management, N. Am. J. Med. Sci. 7 (11) (2015) 483–493.
[29] J. Fong, A. Khan, Hypocalcemia: updates in diagnosis and management for primary care, Can. Fam. Physician 58 (2) (2012) 158–162.
[30] H.R. Pohl, J.S. Wheeler, H.E. Murray, Sodium and potassium in health and disease,

Met Ions Life Sci 13 (2013) 29–47.
[31] T.J. McDonald, R.A. Oram, B. Vaidya, Investigating hyperkalaemia in adults, BMJ 351 (2015) h4762.
[32] E. Kardalas, S.A. Paschou, P. Anagnostis, G. Muscogiuri, G. Siasos, A. Vryonidou, Hypokalemia: a clinical update, Endocr Connect 7 (4) (2018) R135–R146.
[33] A.H. Lichtenstein, L.J. Appel, M. Brands, M. Carnethon, S. Daniels, H.A. Franch, B. Franklin, P. Kris-Etherton, W.S. Harris, B. Howard, N. Karanja, M. Lefevre, L. Rudel, F. Sacks, L. Van Horn, M. Winston, J. Wylie-Rosett, Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association nutrition committee, Circulation 114 (1) (2006) 82–96.
[34] S.A. Muhsin, D.B. Mount, Diagnosis and treatment of hypernatremia, Best Pract Res Clin Endocrinol Metab 30 (2) (2016) 189–203.
[35] R.M. Reynolds, P.L. Padfield, J.R. Seckl, Disorders of sodium balance, BMJ 332 (7543) (2006) 702–705.
[36] D.A. Henry, In the clinic: hyponatremia, Ann. Intern. Med. 163 (3) (2015) ITC1–19.
[37] W.L. Baker, Treating arrhythmias with adjunctive magnesium: identifying future research directions, Eur Heart J Cardiovasc Pharmacother 3 (2) (2017) 108–117.
[38] R.J. Elin, Assessment of magnesium status for diagnosis and therapy, Magnes. Res. 23 (4) (2010) (S194-8).
[39] Y.H. Ko, S. Hong, P.L. Pedersen, Chemical mechanism of ATP synthase. Magnesium plays a pivotal role in formation of the transition state where ATP is synthesized from ADP and inorganic phosphate, J. Biol. Chem. 274 (41) (1999) 28853–28856.
[40] G. van Niekerk, M. Mitchell, A.M. Engelbrecht, Bone resorption: supporting immunometabolism, Biol. Lett. 14 (2) (2018).
[41] W. Jahnen-Dechent, M. Ketteler, Magnesium basics, Clin. Kidney J. 5 (Suppl. 1) (2012) i3–i14.
[42] R. Crichton, Iron Metabolism: From Molecular Mechanisms to Clinical Consequences, John Wiley & Sons, 2016.
[43] R.R. Crichton, R.J. Ward, An overview of iron metabolism: molecular and cellular criteria for the selection of iron chelators, Curr. Med. Chem. 10 (12) (2003) 997–1004.
[44] M. Sánchez, L. Sabio, N. Gálvez, M. Capdevila, J.M. Dominguez-Vera, Iron chemistry at the service of life, IUBMB Life 69 (6) (2017) 382–388.
[45] R.C. Hider, X. Kong, Iron: effect of overload and deficiency, Met Ions Life Sci 13 (2013) 229–294.
[46] J.D. Cook, M.B. Reddy, J. Burri, M.A. Juillerat, R.F. Hurrell, The influence of different cereal grains on iron absorption from infant cereal foods, Am. J. Clin. Nutr. 65 (4) (1997) 964–969.
[47] M. Vasak, D.W. Hasler, Metallothioneins: new functional and structural insights, Curr. Opin. Chem. Biol. 4 (2) (2000) 177–183.
[48] H. Tapiero, K.D. Tew, Trace elements in human physiology and pathology: zinc and metallothioneins, Biomed. Pharmacother. 57 (9) (2003) 399–411.
[49] C.T. Chasapis, A.C. Loutsidou, C.A. Spiliopoulou, M.E. Stefanidou, Zinc and human health: an update, Arch. Toxicol. 86 (4) (2012) 521–534.
[50] A.Q. Truong-Tran, J. Carter, R.E. Ruffin, P.D. Zalewski, The role of zinc in caspase activation and apoptotic cell death, Biometals 14 (3–4) (2001) 315–330.
[51] A.S. Prasad, Discovery of human zinc deficiency: its impact on human health and disease, Adv. Nutr. 4 (2) (2013) 176–190.
[52] N.Z. Gammoh, L. Rink, Zinc in infection and inflammation, Nutrients 9 (6) (2017).
[53] N. Horn, L.B. Møller, V.M. Nurchi, J. Aaseth, Chelating principles in Menkes and Wilson diseases: choosing the right compounds in the right combinations at the right time, J. Inorg. Biochem. 190 (2019) 98–112.
[54] W. Maret, Zinc biochemistry: from a single zinc enzyme to a key element of life, Adv. Nutr. 4 (1) (2013) 82–91.
[55] C. Andreini, L. Banci, I. Bertini, A. Rosato, Counting the zinc-proteins encoded in the human genome, J. Proteome Res. 5 (1) (2006) 196–201.
[56] W. Maret, Zinc in cellular regulation: the nature and significance of “zinc signals”, Int. J. Mol. Sci. 18 (11) (2017).
[57] E.A. Permyakov, R.H. Kretsinger, Cell signaling, beyond cytosolic calcium in eukaryotes, J. Inorg. Biochem. 103 (1) (2009) 77–86.
[58] W. Maret, Molecular aspects of zinc signals, in: T. Fukada, T. Kambe (Eds.), Zinc Signals in Cellular Functions and Disorders, Springer Japan, Tokyo, 2014, pp. 7–26.
[59] Linder, M. C., Biochemistry of Copper. Springer Science & Business Media: 2013; Vol. vol. 10.
[60] L.V. Puchkova, P.S. Babich, Y.A. Zatulovskaia, E.Y. Ilyechova, F. Di Sole, Copper metabolism of newborns is adapted to milk ceruloplasmin as a nutritive source of copper: overview of the current data, Nutrients 10 (11) (2018).
[61] A. Messerschmidt, Handbook of Metalloproteins, Wiley, 2001.
[62] E.I. Solomon, Spectroscopic methods in bioinorganic chemistry: blue to green to red copper sites, Inorg. Chem. 45 (20) (2006) 8012–8025.
[63] G.C. Steffens, T. Soulimane, G. Wolff, G. Buse, Stoichiometry and redox behaviour of metals in cytochrome-c oxidase, Eur. J. Biochem. 213 (3) (1993) 1149–1157.
[64] N.J. Robinson, D.R. Winge, Copper metallochaperones, Annu. Rev. Biochem. 79 (2010) 537–562.
[65] I. Fridovich, The biology of oxygen radicals, Science 201 (4359) (1978) 875–880.
[66] K. Davies, Cloning the Menkes disease gene, Nature 361 (6407) (1993) 98.
[67] S.R. Jaiser, G.P. Winston, Copper deficiency myelopathy, J. Neurol. 257 (6) (2010) 869–881.
[68] A. Aggarwal, M. Bhatt, Update on Wilson disease, Int. Rev. Neurobiol. 110 (2013) 313–348.
[69] P. Chellan, P.J. Sadler, The elements of life and medicines, Philos Trans A Math Phys Eng Sci 373 (2037) (2015).
[70] P. Chen, J. Bornhorst, M. Aschner, Manganese metabolism in humans, Front Biosci (Landmark Ed) 23 (2018) 1655–1679.
[71] J.I. Lachowicz, V.M. Nurchi, G. Crisponi, I. Cappai, R. Cappai, M. Busato, A. Melchior, M. Tolazzi, M. Peana, E. Garribba, M.A. Zoroddu, P. Coni, G. Pichiri, J. Aaseth, Para-aminosalicylic acid in the treatment of manganese toxicity. Complexation of Mn2+ with 4-amino-2-hydroxybenzoic acid and its N-acetylated metabolite, New J. Chem. 42 (10) (2018) 8035–8049.
[72] K.J. Horning, S.W. Caito, K.G. Tipps, A.B. Bowman, M. Aschner, Manganese is essential for neuronal health, Annu. Rev. Nutr. 35 (1) (2015) 71–108.
[73] A.B. Bowman, G.F. Kwakye, E. Herrero Hernandez, M. Aschner, Role of manganese in neurodegenerative diseases, J. Trace Elem. Med. Biol. 25 (4) (2011) 191–203.
[74] H. Fujishiro, M. Doi, S. Enomoto, S. Himeno, High sensitivity of RBL-2H3 cells to cadmium and manganese: an implication of the role of ZIP8, Metallomics 3 (7) (2011) 710–718.
[75] J.S. Crossgrove, R.A. Yokel, Manganese distribution across the blood-brain barrier III. The divalent metal transporter-1 is not the major mechanism mediating brain manganese uptake, NeuroToxicology 25 (3) (2004) 451–460.
[76] J.H. Park, M. Hogrebe, M. Gruneberg, I. DuChesne, A.L. von der Heiden, J. Reunert, K.P. Schlingmann, K.M. Boycott, C.L. Beaulieu, A.A. Mhanni, A.M. Innes, K. Hortnagel, S. Biskup, E.M. Gleixner, G. Kurlemann, B. Fiedler, H. Omran, F. Rutsch, Y. Wada, K. Tsiakas, R. Santer, D.W. Nebert, S. Rust, T. Marquardt, SLC39A8 deficiency: a disorder of manganese transport and glycosylation, Am. J. Hum. Genet. 97 (6) (2015) 894–903.
[77] Q. Ye, J.E. Park, K. Gugnani, S. Betharia, A. Pino-Figueroa, J. Kim, Influence of iron metabolism on manganese transport and toxicity, Metallomics 9 (8) (2017) 1028–1046.
[78] G. Schwarz, A.A. Belaidi, Molybdenum in human health and disease, Met Ions Life Sci 13 (2013) 415–450.
[79] J.L. Burguera, M. Burguera, Molybdenum in human whole blood of adult residents of the Merida State (Venezuela), J. Trace Elem. Med. Biol. 21 (3) (2007) 178–183.
[80] F. Laulicht, J. Brocato, L. Cartularo, J. Vaughan, F. Wu, T. Kluz, H. Sun, B.A. Oksuz, S. Shen, M. Peana, S. Medici, M.A. Zoroddu, M. Costa, Tungsten-induced carcinogenesis in human bronchial epithelial cells, Toxicol. Appl. Pharmacol. 288 (1) (2015) 33–39.
[81] M.A. Zoroddu, S. Medici, M. Peana, V.M. Nurchi, J.I. Lachowicz, F. Laulicht-Glickc, M. Costa, Tungsten or Wolfram: friend or foe? Curr. Med. Chem. 25 (1) (2018) 65–74.
[82] R. Hille, The mononuclear molybdenum enzymes, Chem. Rev. 96 (7) (1996) 2757–2816.
[83] R. Hille, J. Hall, P. Basu, The mononuclear molybdenum enzymes, Chem. Rev. 114 (7) (2014) 3963–4038.
[84] M.J. Romao, M. Archer, I. Moura, J.J. Moura, J. LeGall, R. Engh, M. Schneider, P. Hof, R. Huber, Crystal structure of the xanthine oxidase-related aldehyde oxidoreductase from D. gigas, Science 270 (5239) (1995) 1170–1176.
[85] J. Kuper, A. Llamas, H.J. Hecht, R.R. Mendel, G. Schwarz, Structure of the molybdopterin-bound Cnx1G domain links molybdenum and copper metabolism, Nature 430 (7001) (2004) 803–806.
[86] G. Schwarz, R.R. Mendel, M.W. Ribbe, Molybdenum cofactors, enzymes and pathways, Nature 460 (7257) (2009) 839–847.
[87] S.R. Panneerselvam, S. Govindasamy, Effect of sodium molybdate on the status of lipids, lipid peroxidation and antioxidant systems in alloxan-induced diabetic rats, Clin. Chim. Acta 345 (1–2) (2004) 93–98.
[88] N.F. Suttle, Copper imbalances in ruminants and humans: unexpected common ground, Adv. Nutr. 3 (5) (2012) 666–674.
[89] H. Schjønsby, Vitamin B12 absorption and malabsorption, Gut 30 (12) (1989) 1686–1691.
[90] R. Moll, B. Davis, Iron, vitamin B12 and folate, Medicine 45 (4) (2017) 198–203.
[91] F.S. Mathews, M.M. Gordon, Z. Chen, K.R. Rajashankar, S.E. Ealick, D.H. Alpers, N. Sukumar, Crystal structure of human intrinsic factor: cobalamin complex at 2.6-A resolution, Proc. Natl. Acad. Sci. U. S. A. 104 (44) (2007) 17311–17316.
[92] K. Yamada, Cobalt: its role in health and disease, in: A. Sigel, H. Sigel, R.K.O. Sigel (Eds.), Interrelations between Essential Metal Ions and Human Diseases, Springer Netherlands, Dordrecht, 2013, pp. 295–320.
[93] R. Kozyraki, O. Cases, Vitamin B12 absorption: mammalian physiology and acquired and inherited disorders, Biochimie 95 (5) (2013) 1002–1007.
[94] S.P. Epstein, Y.Y. Pashinsky, D. Gershon, I. Winicov, C. Srivilasa, K.J. Kristic, P.A. Asbell, Efficacy of topical cobalt chelate CTC-96 against adenovirus in a cell culture model and against adenovirus keratoconjunctivitis in a rabbit model, BMC Ophthalmol. 6 (2006) 22.
[95] J. Emsley, Molecules at an Exhibition: Portraits of Intriguing Materials in Everyday Life, OUP, Oxford, 1999.
[96] W. Mertz, The essential trace elements, Science 213 (4514) (1981) 1332–1338.
[97] R. Cornelis, M. Nordberg, Chapter 2 - general chemistry, sampling, analytical methods, and speciation**partly based on Chapter 2: General chemistry of metals by V. Vouk and Chapter 3: Sampling and analytical methods by T. J. Kneip and L. Friberg in Friberg et al. (1986), in: G.F. Nordberg, B.A. Fowler, M. Nordberg, L.T. Friberg (Eds.), Handbook on the Toxicology of Metals, Third edition, Academic Press, Burlington, 2007, pp. 11–38.
[98] D.G. Barnes, M. Dourson, P. Preuss, J. Bellin, C. Derosa, R. Engler, L. Erdreich, T. Farber, P. Fenner-Crisp, E. Francis, G. Ghali, R. Hill, S. Irene, W. Marcus, D. Patrick, S. Perlin, A. Revesz, R. Rubenstein, J. Stara, J. Wiltse, L. Zaragosa, Reference dose (RfD): description and use in health risk assessments, Regul. Toxicol. Pharmacol. 8 (4) (1988) 471–486.
[99] J. Aaseth, L. Gerhardsson, M.A. Skaug, J. Alexander, Chapter 1 - general chemistry of metal toxicity and basis for metal complexation, in: J. Aaseth, G. Crisponi, O. Andersen (Eds.), Chelation Therapy in the Treatment of Metal Intoxication,

Academic Press, Boston, 2016, pp. 1–33.
[100] Scientific opinion on lead in food, EFSA J. 8 (4) (2010) 1570.
[101] Lead exposure in children: prevention, detection, and management, Pediatrics 116 (4) (2005) 1036–1046.
[102] S. Medici, M. Peana, V.M. Nurchi, J.I. Lachowicz, G. Crisponi, M.A. Zoroddu, Noble metals in medicine: latest advances, Coord. Chem. Rev. 284 (2015) 329–350.
[103] S. Medici, M. Peana, G. Crisponi, V.M. Nurchi, J.I. Lachowicz, M. Remelli, M.A. Zoroddu, Silver coordination compounds: a new horizon in medicine, Coord. Chem. Rev. 327-328 (2016) 349–359.
[104] S. Medici, M. Peana, V.M. Nurchi, M.A. Zoroddu, Medical uses of silver: history, myths, and scientific evidence, J. Med. Chem. (2019), https://doi.org/10.1021/acs.jmedchem.8b01439.