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Relationship of trace elements and toxic elements in humans' health

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Abstract

Elements which are detected in small but not precisely known amounts in the living body were called "trace elements" in the past. Recent advances in analytical technologies, such as the development of atomic absorption spectrometry, have made it possible to measure these elements precisely and to determine their functions and the characteristics of their deficiency and excess states. The so-called vitamin boom has passed, and it now appears to be boom-time for trace elements. Nowadays, cases with trace element deficiencies are often encountered clinically, especially during high-calorie parenteral therapy or enteral nutrition, and congenital abnormalities of trace element metabolism have been clarified successively. Thus, knowledge of the clinical aspects of trace elements is becoming indispensable for front-line clinicians. Meanwhile, epidemiological surveys and animal studies have suggested the possibility that some trace element deficiencies are associated with a reduced anti-oxidant potential in organisms (which is believed to possibly underlie the onset of cancer and atherosclerosis), accelerated aging, developmental retardation in children, and an increased incidence of abnormal pregnancies, immunological abnormalities, and lifestyle-related diseases.

Thus, from the viewpoint of prophylactic medicine, study, survey, and prophylaxis of trace elements are also attracting close attention. Some Heavy metals have bio-importance as trace elements but the biotoxic effects of many of them in human biochemistry are of great concern. Hence, there is a need for proper understanding of mechanism involved, such as the concentrations and oxidation states, which make them harmful. It is also important to know their sources, leaching processes, chemical conversions and their modes of deposition in polluting the environment, which essentially supports life. Literature sources point to the fact that these metals are released into the environment by both natural and anthropogenic means, especially mining and industrial activities, and automobile exhausts. They leach into the underground waters, moving along water pathways and eventually depositing in the aquifer, or are washed away by run-off into surface waters thereby resulting in water and subsequently soil pollution. Poisoning and toxicity in ecosystem occur frequently through exchange and co-ordination mechanisms. When ingested, they form stable biotoxic compounds, thereby mutilating their structures and hindering bioreactions of their function.

Keywords: Trace elements; Lung Cancer; Copper; Iron

1. Introduction

Cancer is a multifactorial disease causing 9.6 million deaths annually, Both sexes combined, the most common organs susceptible to cancer development are lung (LC), breast (BC), prostate (PC), and colon/rectum (CRC), Cancer is characterized by a progressive transformation of healthy cells into malignant progeny. During this process, tumor cells acquire novel properties over time resulting in e.g., unrestricted proliferation and invasion capacity which have been summarized in the so-called 'hallmarks of cancer' [1,2].

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In general, progression of cancer is expressed as cancer stages, reflecting the spread of tumors from unspread (I) to growing tumors penetrating in the adjacent tissues (II-III) or other organs (IV). Depending on the tumor type, these different stages can be identified and characterized by changes of tumor biomarkers, e.g., K-Ras, HER2/NEU or different cancer antigens. As early diagnosis is one of the most important contributors to a successful cancer therapy, there is an urgent need for further reliable biomarkers for detection of malignant cells in the body[3]. During the last decades, the focus was mainly on the identification of mutations in driver genes which were both used for diagnostics but also for a personalized tumor therapy. Besides genetic modifications, tumor cells are characterized by substantial changes in their metabolism affecting the need for macronutrients but also for micronutrients. Already in 1975, Schwartz reviewed the role of trace elements (TEs) including copper (Cu), selenium (Se), and zinc (Zn) in cancer, discussing their potential roles as diagnostic or prognostic markers. In this mini review, we aim to extend the current view by further testing the hypothesis whether concentrations of the TEs Se, iron (Fe), Cu, and Zn are suitable predictors for the diagnosis of cancer [4,5].

To do so, recently published case-control studies of the most common cancer types that determined TE concentrations in serum/plasma or within the tumor tissue were selected. As the measurement of total TE concentrations might not appropriately indicate functional impairments, as reported e.g., for Zn, also biomarkers are used for describing the TE status. While selenoproteins such as selenoprotein P (SELENOP) and plasma glutathione peroxidase (GPX3) are frequently used to analyse the Se status, the Cu status can additionally be described by ceruloplasmin concentrations [6,7]. For Zn, the amount of free Zn in serum is discussed as more appropriate biomarker but this still needs to be validated further. Next to the Fe concentration itself, the Fe storage and transport proteins ferritin and transferrin, respectively, are used to assess the Fe status. Further biomarkers include total Fe binding capacity (TIBC), indicating the capacity of transferrin to bind Fe, and transferrin saturation (TSAT), calculated by dividing serum Fe by TIBC. However, several of these biomarkers are frequently distorted by other clinical factors e.g., inflammation, hydration status or hemolysis (in case of serum Fe), resulting in incorrect conclusions regarding the patient's TE status The physiological reference ranges for the considered TEs are given in Table 1[8,9].

Table 1 Reference ranges for the trace elements selenium (Se), iron (Fe), copper (Cu), and zinc (Zn).

Trace element	Reference ranges in serum	Reference
Se	70-150 µg/l	[11]
Fe	men: 0.55–1.60 mg/l women: 0.40–1.55 mg/l	[12]
Cu	0.64–1.40 mg/l	[12]
Zn	0.66–1.10 mg/l	[13]

1.1. Classification of trace elements

Twenty-nine types of elements present in the human body have been classified into five major groups as follows:

- Group I: basic components of macromolecules such as carbohydrates, proteins, and lipids. Examples include carbon, hydrogen, oxygen, and nitrogen.
- Group II: nutritionally important minerals also referred to as principal or macroelements. The daily requirement of these macroelements for an adult person is above 100 mg/day. Examples include sodium, potassium, chloride, calcium, phosphorous, magnesium, and sulfur[10].
- Group III: essential trace elements. The trace elements are also called minor elements. An element is considered a trace element when its requirement per day is below 100 mg. The deficiency of these elements is rare but may prove fatal. Examples include copper, iron, zinc, chromium, cobalt, iodine, molybdenum, and selenium[6].
- Group IV: additional trace elements. Their role is yet unclear and they may be essential. Examples include cadmium, nickel, silica, tin, vanadium, and aluminum. This group may be equivalent to probably essential trace elements in the WHO classification.
- Group V: these metals are not essential and their functions are not known. They may produce toxicity in excess amounts. Examples include gold, mercury, and lead. This group is equivalent to potentially toxic elements defined in the WHO classification[11].

1.2. Essential trace elements

The essential trace elements are broadly categorized into macro elements and trace or microelements.The trace elements in human enzyme system

1.2.1. Copper (Cu)

Copper plays a very important role in our metabolism largely because it allows many critical enzymes to function properly. Acidic conditions promotes the solubility which incorporates copper ions either in cupric form or cuprous form into the food chain. Copper toxicosis in plants is very rare compared to its deficiency while in animals and man toxicosis is usually induced by environmental concentrations in genetically abnormal individual. Mainly copper is available in the liver, shellfish, dried fruit, milk and milk products, sunflower seeds, oysters, sesame seeds, tahini, and sun dried tomatoes. he average content of metal in the plant usually ranges from 4 to 20 mg of copper per kg of dry weight[12]. The average adult human of 70 kg weight contains about 100 mg. The daily requirement is about 2-5 mg of which 50% is absorbed from the gastrointestinal tract (GIT). Rest is excreted via bile and kidney. Copper accumulates in the liver, brain and kidney more than rest of body. Over 90% of plasma copper is associated with ceruloplasmin and 60% of red blood cell (RBC) is bound to superoxide dismutase.

In human blood, copper is principally distributed between the erythrocytes and in the plasma. In erythrocytes, 60% of copper occurs as the copper-zinc metalloenzyme superoxide dismutase, the remaining 40% is loosely bound to other proteins and amino acids[13]. Total erythrocytes copper in normal human is around 0.9-1.0 pg/ml of packed red cells. Copper has a selected biochemical function in hemoglobin (Hb) synthesis, connective tissue metabolism, and bone development. Synthesis of tryptophan is done in the presence of Cu. Besides these Cu as ceruloplasmin aid in the transport of iron to cells. A deficiency of Cu in diet for prolonged period especially during stages of active growth leads to anemia, growth retardation, defective keratinization and pigmentation of hair, hypothermia, mental retardation, changes in skeletal system, and degenerative changes in aortic elastin.

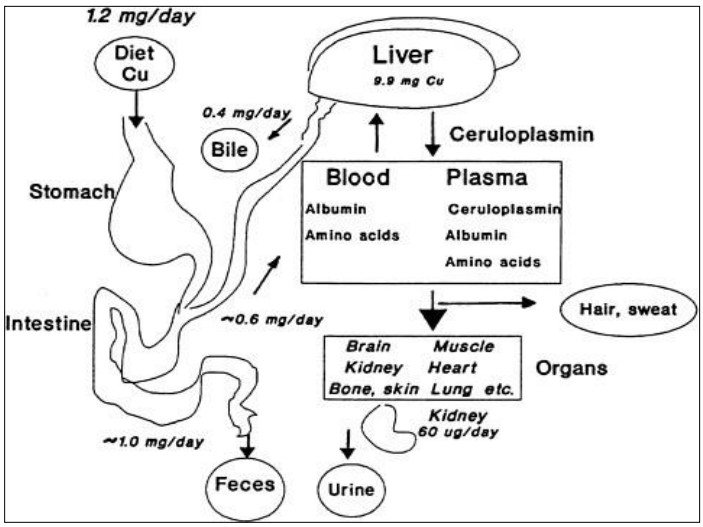

Figure 1 Overview of copper absorption, transport, and excretion

Excessive Cu either from diet or through any other sources acquired rapidly produces nausea, vomiting, diarrhea, profuse sweating, and renal dysfunction. When the levels of Cu are acquired very slowly, stage theycause cirrhosis, hepatitis, tremors, mental detritions, Kayser–Fleischer rings, hemolytic anemia, GIT bleeding and azotemia. Congenital diseases like Wilson's disease, Menken's syndrome, idiopathic fibrosis of lung has been associated with Cu. Vineyard sprayer's lung diseases is an occupational hazard due to Cu intake via aerosol which 75% is in blood. The serum levels of copper increases in patients with myocardial infarction, leukemia, solid tumors, infections, cirrhosis of liver, hemochromatosis, thyrotoxicosis, and computed tomography disorders. Decreased levels occur in nephritic syndrome, Kwashiorkor, Wilson's disease, severe diarrhea, and vomiting[14]. The symptoms of copper deficiency are hypochromic anemia, neutropenia, hypopigmentation of hair and skin, abnormal bone formation with skeletal fragility and osteoporosis, joint pain, lowered immunity, vascular abnormalities, and uncrimped or steely hair. High copper intake for prolonged period causes increased copper percentages in serum and tissue that in turn causes oxidative stress and affects several immune functions. Decreased copper levels are observed in few malignancies, mostly in the tumors which have high catabolic rate or which is of highly metastatic type. Some of the trace elements like copper and zinc

have an anticarcinogenic role. Copper is involved in the cell metabolism, and is a part of various enzymes such as tyrosinase, uricase, and cytochrome oxidase, which are mainly concerned with oxidation reaction. The mean serum copper levels were significantly higher in the sera of patients with oral potentially malignant disorder[15].

1.2.2. Iron (Fe)

Iron is present in huge quantities all over the earth crust and also is available to a great extent from the plant kingdom. Acidic condition promotes the solubility of iron as ions either in ferric or ferrous forms. The total body content of iron is about 3-5 g of which 75% is in blood while the rest is in liver, bone marrow and muscles.Heme is the major iron containing substance[16].

It is found in Hb, myoglobin, cytochrome while the enzymes associated with iron are cytochrome A, B, C, F 450, cytochrome C reductase, catalases, peroxidases, xanthine oxidases, tryptophan pyrrolase, succinate dehydrogenase, glucose 6 phosphate dehydrogenase, and choline dehydrogenase.An average daily requirement is 1-2 mg which has to provide as 20 mg of iron in food. Phytates and oxalates reduce the iron absorption in the GIT. Iron is absorbed from food when there is a need and the transport form of iron is known as ferritin. Hemosiderin is a golden brown pigment seen in cells of the reticuloendothelial system which is denatured form of ferritin. The metabolism of iron is unique because it maintains homeostasis by regulating the absorption of iron but not excretion. When iron stores in the body are depleted, absorption is enhanced. Deficiency of such an important trace metal will cause severe disorders, most important among them is iron deficiency anemia. Microcytic hypochromic RBC's, tiredness, achlorhydria, Plummer–Vinson syndrome, atrophy of epithelium, impaired attention, irritability, and lowered memory are some of the features of iron deficiency anemia. Iron deficiency anemia can lead to heart failure[17]. Anemia is the second most important cause of maternal mortality in India and it is estimated that about 20% of maternal deaths are directly related to anemia and another 50% of maternal deaths are associated with it. The deficiency when prolonged will be fatal. When iron is increased in body acutely, nausea, vomiting, diarrhea occurs along with hepatic damage. While chronic or prolonged accumulation of iron in body occurs there is a hepatic failure, diabetes, testicular atrophy, arthritis, cardiomyopathy, peripheral neuropathy, and hyperpigmentation. Bronze diabetes is a triad of hemochromatosis, diabetes, and cirrhosis. The hepatic peptide hepcidin is an important systemic iron regulatory hormone. It regulates intestinal iron absorption, plasma iron concentrations, and tissue iron distribution by inducing degradation of its receptor and the cellular iron exporter ferroportin. Ferroportin exports iron into plasma from absorptive enterocytes, from macrophages that recycle the iron from senescent erythrocytes, and from hepatocytes that store iron[18].

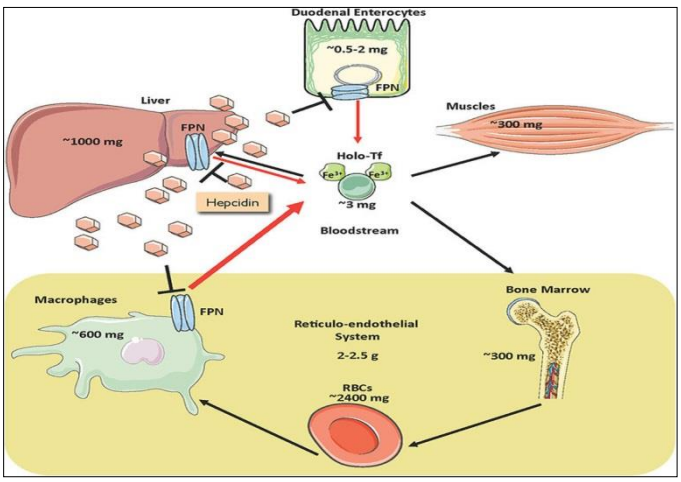

Figure 2 Distribution of iron in the adult human body and regulation of iron traffic.

Deficiency of hepcidin causes hemochromatosis. There are very few genetic disorders related to iron. One of them is due to an abnormal gene located on short arm of chromosome number 6 and linked to human leukocyte antigen — A locus.The erythropoietin may be inhibited by cytokines such as interleukin 1, 6, tumor necrosis factor α, and interference. Serum ferritin levels are elevated, serum iron concentrations are decreased with tumor progression in head and neck carcinomas and thus it can be used as a follow-up tool for patients.There are studies related to potentially malignant disorders and iron. In oral submucous fibrosis and oral leukoplakia, there is a signifi can't decrease in Hb and serum iron, whereas in oral submucous fibrosis the total iron binding capacity showed statistically significant changes. Recently, it has been found that iron may play a role in esophageal carcinogenesis[18].

1.2.3. Zinc (Zn)

The metal zinc is an omnipotent metal that has amphoteric nature. Hence, it is ionized either in acidic or alkaline forms. Content of zinc is 2-3 ng the average body content of zinc is 2-3 g in an average adult. About 99% is intracellular while the rest is in plasma. The average daily requirement is 15-20 mg/day. Phytase decreases fibers, phosphates, calcium, and copper competes with zinc for absorption from small intestine.About 2-5 mg/day is excreted via pancreas and intestine[13] The other mode of excretion is via proximal tubule and sweat glands.Plasma zinc levels are decreased in pregnancy, fl uid loss, oral contraceptive usage, blood loss, acute myocardial infarction, infections, and malignancies.The function of zinc in cells and tissues is dependent on metalloproteinase and these enzymes are associated with reproductive, neurological, immune, dermatological systems, and GIT[20].

It is essential for normal spermatogenesis and maturation, genomic integrity of sperm, for normal organogenesis, proper functioning of neurotransmitters, proper development of thymus, proper epithelialization in wound healing, taste sensation, and secretion of pancreas and gastric enzymes. They can be biochemically classified as those involved in nucleic acid and protein synthesis and degradation, alcohol metabolism, carbohydrate, lipid, and protein metabolism[19]. They include transferases, hydrases, lyses, isomerizes oxidoreductases, and transcription factors. The enzyme most essential for zinc are alkaline phosphates, alcohol dehydrogenase, carboanhydrase, glutamate and lactase dehydrogenase, and RNA polymerases.

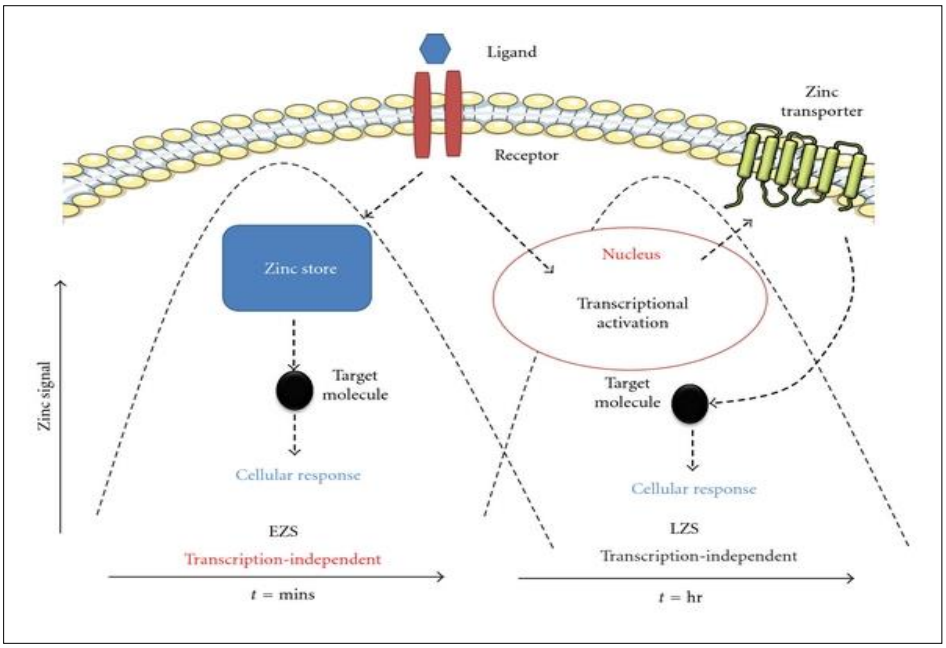

Figure 3 Early zinc signaling (EZS) and late zinc signaling (LZS). EZS involves transcription-independent mechanisms where an extracellular stimulus directly induces an increase in zinc levels within several minutes by releasing zinc from intracellular stores

The deficiency symptoms include compromised energy metabolism, alcohol intoxication, acidosis, blockage of protein biosynthesis, transmutation reaction blocked cell destruction by superoxide radicals. Zinc plays an important role in cell proliferation, differentiation and metabolic activity of the cell[20]. These modifications will take place in the presence of many zinc-binding proteins. Intracellular zinc is homeostatically maintained at extremely low levels either by sequestration in intracellular vesicles or binding to intracellular metalloproteinase and low molecular weight ligands[21]. Zinc plays an important role in the proliferation, differentiation, and metabolic function of mammalian cells. Various extracellular signals, e.g., redox stress, cytokines, and growth factors stimulate the release of zinc from metallothionein or alter the transport of zinc which alters the intracellular level of mobile reactive zinc. Zinc then binds to and activates metal responsive transcription factors or interacts directly with intracellular signaling molecules to modulate the expression of zinc-responsive genes and to regulate specifi c signal transduction pathways. Mutations that activate H-Ras are oncogenic in most cells and lead to malignant transformation and this Ras signaling pathway is inhibited by zinc[21].

1.2.4. Chromium (Cr)

Chromium word is derived from Greek in which chrome means "color". First identifi ed as PbCro4. Full name of chromium is chromium acetylacetonate. The total content of chromium is about 0.006 g in an average human adult. The daily requirement is about 0.005 mg/day. The need of chromium is for biosynthesis of glucose tolerance factor. The deficiency causes impairment of glucose tolerance while toxicity results in renal failure, dermatitis, and pulmonary cancer. Processed meats, whole grain products, pulses, and spices are the best sources of chromium, while dairy products and most fruits and vegetables contain only small amounts. Chromium content in animal foodstuff such as meat, poultry, and fish is low which provides 2 μg Cr[11].Chromium deficiency is diffi cult to document because of the very low levels present in blood, while tissue levels are 10 times higher. If concentrations of chromium are lower than the normal value of 0.14-0.15 ng/ml for serum or 0.26 or 0.28 ng/ml for plasma it indicates the presence of a severe chromium deficiency.

Raised plasma levels can coexist with a negative balance. Hyperglycemia may be associated with raised plasma chromium and increased urinary excretion, without reflecting tissue level. Chromium concentrations in urine, hair, and other tissues or body fluids have also been reported not to reflect chromium status[22]. The role of chromium supplementation was investigated in special subgroups of patients with diabetes. Longstanding exposure with chromium will cause chronic ulcers of the skin and acute irrelative dermatitis have been consistently reported in workers exposed to chromium containing materials. Inhalation of Chromium compounds causes marked irritation of the respiratory tract. Rhinitis, bronchospasm, and pneumonia.Chromium is considered to be a one of the risk factor for oral squamous cell carcinoma. Welding fumes involves exposure to many chemicals, including metal dust, irritant gases. Welding in stainless steel is associated with an increased risk of cancer of larynx and pharynx due to exposure to hexavalent chromium[23].

1.2.5. Cobalt

The average human adult contain about 1.1 g with the daily requirement of 0.0001 mg/day. It is a component of Vitamin B12. It induces erythropoietin and blocks iodine uptake by the thyroid. It has a role to play in methionine metabolism where it controls the transfer of enzymes like homocysteine methyl transferees. Deficiency produces cardiomyopathy, congestive cardiac failure, pericardial effusion, polycythemia, and thyroid enlargement[24]. The occurrence of cobalt in animal tissues was demonstrated by Bertrand and Macheboeuf in 1925 and a wide distribution was confirmed by other workers employing spectrographic methods. Cobalt is usually found in the environment combined with other elements such as oxygen, sulfur, and arsenic. Small amounts of these chemical compounds can be found in rocks, soil, plants, and animals. Most of the production of cobalt involves the metallic form used in the formation of cobalt super alloys.

The term "hard metal" refers to compounds containing tungsten carbide (80-95%) combined with matrices formed from cobalt (5-20%) and nickel (0-5%). For the general population, the diet is the main source of exposure to cobalt[25]. Meat, liver, kidney, clams, oysters, and milk all contain some cobalt. Ocean fish and sea vegetables have cobalt, but land vegetables have very little; some cobalt is available in legumes, spinach, cabbage, lettuce, beet greens, and figs. The recommended daily intake of Vitamin B12 for an adult in the USA was said to be 3 μg, corresponding to 0.012 μg of cobalt. Cobalt compounds are absorbed by the oral and inhalation routes and through the skin. The degree of gastrointestinal absorption depends on the dose; very small doses in the order of a few μg/kg are absorbed almost completely, whereas larger doses are less well absorbed. Cobalt is not easily absorbed from the digestive tract[26].

The body level of cobalt normally measures 80-300 mcg. It is stored in the RBCs and the plasma, as well as in the liver, kidney, spleen, and pancreas. Cobalt has both beneficial and harmful effects on human health. Cobalt is beneficial for humans because it is part of Vitamin B12, which is essential to maintain human health. Cobalt (0.16-1.0 mg cobalt/kg of body weight) has also been used as a treatment for anemia, including in pregnant women because it causes erythropoiesis. Cobalt also increases RBC production in healthy people, but only at very high exposure levels. Deficiency of cobalt also leads to fatigue, digestive disorders, and neuromuscular problems. As cobalt's deficiency leads to decreased availability of B12, there is an increase of many symptoms and problems related to B12 deficiency, particularly pernicious anemia, and nerve damage. Cobalt is excreted in both the urine and the feces, independent to the route of exposure (inhalation, injection or ingestion) most. cobalt will be eliminated rapidly. In one cohort study of people with hip prosthesis, there was a significant increase in the incidence of lymphatic and hematopoietic malignancies, and significant deficits of breast and colorectal cancer[27].

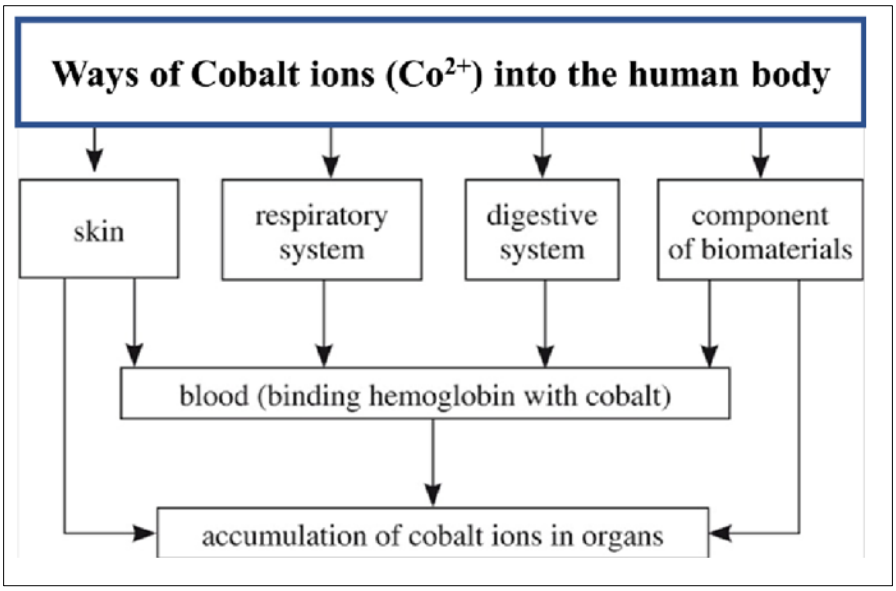

Figure 4 Ways of cobalt ions into body. The largest source of exposure to cobalt for the general population is the food supply**.**

1.2.6. Manganese (Mn)

Manganese content of foods varies greatly. Peterson and Skinner and Schroeder et al. found the highest concentrations in nuts, grains, and cereals; the lowest in dairy products, meat, poultry, fish, and seafood. Relatively high concentrations of manganese were found in soluble ("instant") coffee and tea and account for 10% of the total daily intake. The total body content average human adult has about 15 mg of manganese, typically seen in nucleic acid. Daily requirement is about 2-5 mg/day. Manganese acts as an activator of enzyme and as a component of metalloenzymes[28]. They have a role to play in oxidative phosphorylation, fatty acids and cholesterol metabolism, mucopolysaccharide metabolism, and urea cycle. Manganese is found in all mammalian tissues with concentrations ranging from 0.3 to 2.9 μg manganese/g.

Tissues rich in mitochondria and pigments (e.g., retina, dark skin) tend to have high manganese concentrations. Bone, liver, pancreas, and kidney typically have higher manganese concentrations than other tissues. The largest tissue store of manganese is in the bone. Bone, liver, pancreas, and kidney typically have higher manganese concentrations than other tissues. The largest tissue store of manganese is in the bone.In hydroxyapatite crystals of enamel, more than 49 elements are found, one of them being manganese, mostly in very small percentage[29]. The concentrations of manganese in enamel are 0.08-20 ppm, equivalent 0.08-20 mg/kg, and in dentine are from 0.6 to 1000 ppm. Mn concentration is higher in the outer surface of enamel than in enamel-dentin border, and higher in permanent than in primary dentition. Some of the enzymes which are present along with magnesium are arginase, diamine oxidase, pyruvate carboxylate, phosphoglucomutase, succinate dehydrogenase, glutamine synthetase, superoxide dismutase. The defi ciency cause bleeding disorders due to increased prothrombin time while accumulation over a long period causes anorexia, apathy, headache impotence, leg cramps, speech disturbance, encephalitis like syndrome and parkinsonian like syndrome. Psychosis may also occur[30].

1.2.7. Selenium

The relationship between selenium and oral cancer has not yet been understood clearly, but there is some evidence observed that there is a relationship between selenium and Keshan syndrome. Few studies have shown that prolonged deficiency of selenium produces this syndrome's features in animals such as failure growth in rats and muscle diseases in sheep. A selenium responsive clinical syndrome in humans is described in some pathological conditions. In humans, they observed that those who take oral self-medication containing selenium causes muscular complications[31]. Low blood levels of selenium observed in some pathological conditions such as colonic, gastric and pancreatic carcinoma and cirrhosis. Increased selenium intake may cause Keshan syndrome. Keshan disease was first described in 1935 in North China. Clinically Keshan disease showed acute and chronic episodes of cardiogenic shock, enlarged heart, congestive heart failure, and cardiac arrhythmias. The etiology of Keshan disease is still perplexing. There are numerous hypothesis suggested by different studies such as viral infections, environmental intoxication, mycotoxins, and nutritional deficiency. The hypothesis that relates with the deficiency of selenium is the most accepted hypothesis[32]

1.2.8. Fluorine

Fluorine is a lightest element in Group VII of the periodic table, with atomic number 9.Fluorine plays an important role in the hard tissues of the body such as bone and teeth. It helps in producing denser bones and fluoride has been suggested as a therapeutic agent in the treatment of osteoporosis. It is thought that fluoride, in conjunction with calcium, stimulates osteoblastic activity. It gets integrated into the bone matrix as fluorapatite which in turn increases the hardness of bones. Fluorine has profound antienzyme properties and prevents dental caries[33]. The increased fluoride utilization could be responsible for the anticariogenic action. Fluoride or fluorine deficiency is a hypothetical disorder, which may cause increased dental caries and possibly osteoporosis due to a lack of fluoride in the diet. High levels of dietary fluoride cause fluorosis (bone disease) and mottling of teeth. High levels of fluoride cause dental lesions, periosteal hyperostosis, calcification of ligaments, and lameness. Crippling fluorosis in human is observed in persons exposed to very high intake (>20 mg/day) over a period of several years. Acute toxicity of fluoride is very rare and can occur due to a single ingestion of a large amount of fluoride and can be fatal.

The amount of fluoride considered lethal when taken orally is 35-70 mg F/kg body weight[34]. Symptoms of acute toxicity occur rapidly. There is a diffuse abdominal pain, diarrhea, vomiting, excess salivation, and thirst. Chronic toxicity is caused due to long-term ingestion of smaller amounts of fluoride in drinking-water. Excessive fluoride more than 8 ppm in drinking water daily for many years can lead to skeletal and dental fluorosis. Severe cases are normally found only in warm climates where drinking-water contains very high levels of fluoride. Due to chronic toxicity, bone density slowly increases; the joints stiffen and become painful. Dental fluorosis may be easily recognized but the skeletal involvement is not clinically obvious until the advanced stage and early cases may be misdiagnosed as rheumatoid arthritis or osteoarthritis. Fluoride increases the stability of the crystal lattice in bone, but makes bone more brittle. The total quantity of fluoride ingested is the single most important factor in determining the clinical course of skeletal fluorosis; the severity of symptoms correlates directly with the level and duration of exposure[35].

1.2.9. Iodine

Iodine is a vital micronutrient required at all stages of life; fetal life and early childhood being the most critical phases of requirement. Iodine is an essential constituent of the thyroid hormones thyroxine (T4 tetraiodothyronine) and (T3 triiodothyronine). It also plays an important role in the functioning of the parathyroid glands. Iodine also promotes s general growth and development within the body as well as aiding in metabolism. Because of its role in the metabolism, the symptoms of an iodine deficiency can be far reaching. Even though it is so important to proper functioning of the human organism, iodine defi ciency is not uncommon[36]. Severe iodine deficiency often occurs in individuals who have thyroid disease and are hyperthyroid or those who have a goiter from thyroid malfunction. Symptoms of iodine defi ciency may include extreme fatigue, slowing of both physical and mental processes, weight gain, facial puffi ness, constipation, and lethargy. Babies born to iodine deficient mothers may be lethargic and difficult to feed. If they are left untreated, it is likely that they will develop cretinism and end up suffering poor overall growth and mental retardation. Iodine overload is less common compared with its deficit though it is unfavorable, as well as a lack of it. The literature provides information demonstrating that intake of iodine from seaweeds is safe because iodine is organically bound and is not cumulated in the body. If its intake is exceeded, it is excreted with urine, mainly during the 1st day. Organically bound iodine is harmless, even with prolonged use at high doses[37]

1.2.10. Lithium (Li)

Lithium (Li), also known as white gold, is a key component of modern “green” batteries, Globally, Li production reached 100,000 metric tons in 2021, a 256% increase from 2010, with 74% of it going into rechargeable Li-ion batteries powering electronic products and electric vehicles , On the one hand, the soaring demand for Li has led to an exponential increase in its supply; on the other hand, electronic waste is increasingly contributing to soil contamination with Li^+ ions or Li_2O[38]. Lubricating grease accounts for 4% of total Li industrial applications and enters the environment through road runoff. Another 14% is used for ceramics and glass production and ends up in municipal waste/landfills, Even Li ingested by humans is excreted through the kidneys within 24 h and is discharged into sewage, Highly variable concentrations of Li in the environment and food products have deleterious effects on animal and human health and represent a growing challenge for regulators[39].

Li is a non-essential micronutrient, but its deficiency causes aggressive behavior, suicidal tendencies, bipolar or unipolar disorder, and acute mania. Li deficiency alters milk production and reproduction patterns in domestic animals. The exact mechanism explaining such events remains unclear. When present at high doses (approximately 17.5–24 mg L^{-1}) in the blood, Li induces visual nausea, impairment, and kidney problems; while beyond 24 mg L^{-1}, it causes cardiac arrest and coma. LiCl toxicity has directly affected testicular tissue function, leading to male infertility via

impaired steroidogenesis and spermatogenesis[39]. Li accumulates in the brain, gills, and kidneys of fish, which may represent a risk to the food chain. The Li concentration in the plants usually lies between 0.2 and 30 mg kg^{-1} due to preferential uptake or exclusion across species. The bioaccumulation of Li depends on the plant species and the location where they are cultivated. Thibon et al. reported Li accumulation in the brain (0.34 mg kg^{-1}), gills (0.26 mg kg^{-1}), kidneys (0.15 mg kg^{-1}), liver (0.07 mg kg^{-1}), and muscles (0.06 mg kg^{-1}) of fish species. Furthermore, the amount of Li in the normal human body is approximately 7.0 mg[38].

Li intake through the food web

Li is emerging as an important trace element in human nutrition, to whom it is available through the food chain. The amount of Li in the human body is approximately 7 mg, with a recommended daily allowance of 1 mg. Li intake through ingestion depends on its concentration in food and varies based on soil Li levels[40].

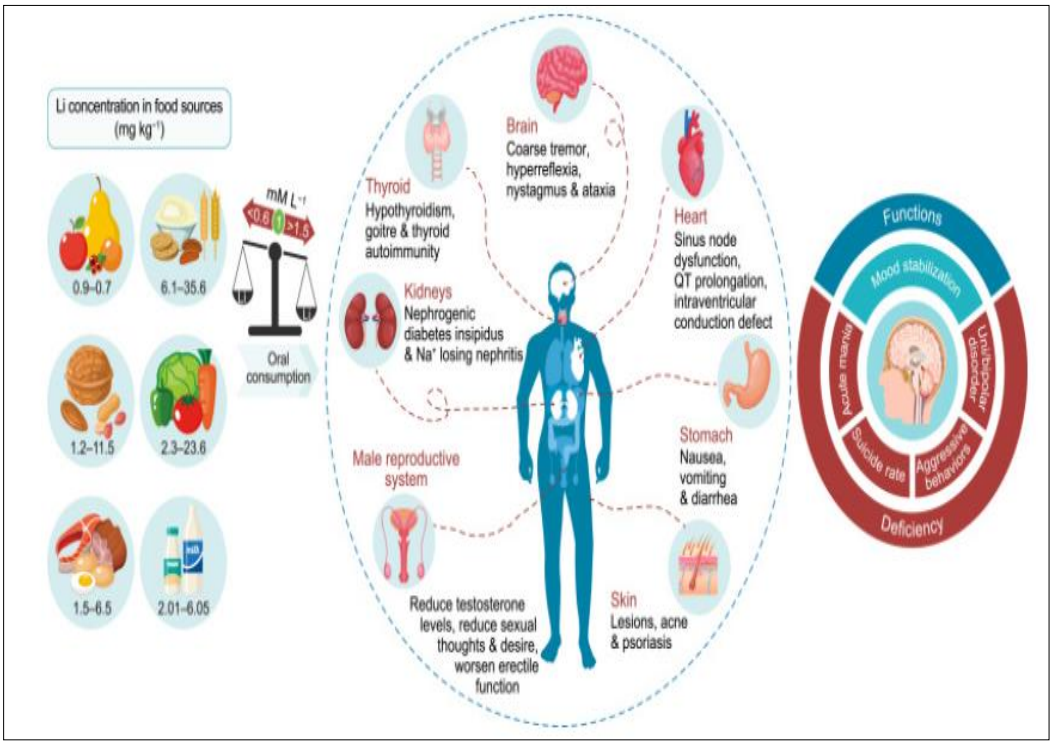

Figure 5 Systematic framework depicting the interplay between Li and human health. The scheme starts with daily intake of Li and includes oral consumption balance and Li functionalities, as well as consequences for the human body.

1.2.11. Consequences of Li exposure on human health

Low levels of Li are associated with higher rates of depression and anxiety, insomnia, sensitivity to stress, chronic pain, and a decline in natural healing processes, memory, and learning ability. Li salts, such as Li_2CO_3 and $LiCH_3COO$, are used to treat manic-depressive disorders; however, off-label therapeutic use of Li_2CO_3 is toxic to the muscular, cardiovascular, gastrointestinal, urinary, and nervous systems in humans, having the potential to cause death [41]Short-term exposure to Li (months to years) causes nephrogenic diabetes insipidus, polyuria, polydipsia, dehydration, a defect in urinary concentration, and thirst. Chronic higher Li dose therapy may increase the chances (6–8 fold) of developing the end-stage renal disease. Moreover, drugs reducing the glomerular filtration rate might inflict chronic toxicity. The lower/higher levels of Li in humans reflect etiological factors for different conditions. Studies should focus on the above diseases and Li deficiency issues to understand the underlying mechanisms[42].

1.2.12. Arsenic (As)

Arsenic is a metalloid, ubiquitously available in the earth's environment and considered to be a global health risk factor. Essentially, arsenic concentrates in earth's crust, bedrocks and leaches gradually into the drinking water. One of the most stable forms of arsenic is ^{75}As isotope and −3, 0, +3 and +5 are some of the common valence states of arsenic. Being a metalloid, arsenic exists in various allotropic forms such as elemental, sulfide and carbonate form. Exposure to inorganic arsenic through consumption of contaminated food, water, air and occupational exposure but not organic

arsenic (majorly seafood such as fish, oysters, prawns, mussels, etc.) leads to serious effects on human health. Low doses and long term exposures of arsenic leads to a range of medical complications termed as "Arsenicosis" [43].

Arsenic exposure is a consequence of natural or anthropogenic sources. Ingestion, inhalation and skin absorption are some of the crucial routes for arsenic entering human body. Both pentavalent and trivalent arsenic compounds are rapidly and extensively absorbed from the gastrointestinal tract. Moreover, sodium arsenate absorption is higher and inorganic tetravalent arsenic is poorly absorbed. However, arsenic trisulfide and lead arsenate are some of the arsenic compounds with lowest rate of oral absorption , Arsenic exposure by inhalation entirely depends on its molecular size. The rate of absorption through inhalation for sodium arsenite, sodium arsenate and arsenic trioxide were rated higher than arsenic sulfide and lead arsenate[44]. Trivalent compounds are more water soluble than pentavalent arsenic compounds and therefore are more toxic in nature. Reduced (trivalent As(III)) and oxidized (pentavalent As(V)) forms of arsenic, maybe absorbed and accumulated in tissues and body fluids.Distribution of arsenic in the body is fairly constant but widely distributed in organs such as skin, lungs, liver and kidneys. In liver, the metabolism of arsenic involves enzymatic and non-enzymatic methylation. Inorganic arsenic is reduced from pentoxide to trioxide via enzymatic or non-enzymatic (glutathione) processes. About 70% Arsenic (both organic and inorganic types) excreted through renal system via urine. Inorganic arsenic (iAs) retains in the body longer than organic arsenic and excretion process of iAs is longer[45].

Low to moderate levels of arsenic exposure (10–300 μg/L) through drinking water has adverse effects such as skin lesions, circulatory disorders, neurological complications, diabetes, respiratory complications, hepatic and renal dysfunction including mortality due to chronic diseases. An estimation of about 100 million population all around the world are exposed to arsenic levels more than 50 μg/L. via drinking water but also through industrial processes. Certain countries such as India, Taiwan, China and Bangladesh are facing serious issues eliminating contamination of arsenic from drinking water sources. Depending on the type of arsenic exposure (i.e. acute or chronic) development of clinical symptoms varies. However, symptoms of acute exposure develop much quicker, whereas clinical symptoms of chronic arsenic exposure develop over a prolonged period of exposure. In acute arsenic toxicity organ damage could occur and may lead to death. On the other hand, disfiguration of extremities due to chronic arsenic exposure may lead to the development of malignant tumors[46]

1.3. Effects of arsenic on Integumentary system

Skin along with its appendages such as hairs and nails forms Integumentary system. It is commonly described as the largest organ of the body. Skin is considered to be more susceptible and highlight initial manifestations of arsenicosis . Skin abnormalities hold the hallmark of chronic arsenic exposure in adults. Moreover, men are likely to develop arsenic induced skin disorders compared to women. Some of the key characteristic features of arsenic

arsenic affects almost all cellular processes and organ functions in our body. Current review manages to highlight certain effects and respective molecular mechanisms of arsenic induced complications in assorted organ systems of human body comprehensively. Moreover, it is clearly evident that in utero exposure to arsenic can induce epigenetic effects and increase disease susceptibility in later stages of life. Development of cancer in skin, lung, liver, bladder, kidney [47].

1.3.1. Mercury (Hg)

Mercury (Hg) is ubiquitously distributed in the environment and is non-essential and toxic to the human body. Mercury is considered to be one of the major environmental pollutants, is widely used in industry, agriculture, and medicine, and circulates in ecosystems, but is never destroyed. Chemically, mercury exists in various forms as elemental (or metallic, Hg^0) mercury, inorganic mercury compounds, and organic mercury compounds. Elemental mercury is liquid at room temperature, and it can be released easily into the atmosphere as mercury vapor because of its high vapor pressure[48]. Inorganic mercury compounds exist in two oxidative states (mercurous, Hg^+; mercuric, Hg^{++}), which are generally in solid states as mercurous or mercuric salts and mercury compounds with chlorine, sulfur, or oxygen. Methylmercury and ethylmercury are common organic forms of mercury combined with carbon. Methylmercury is also formed from methylation of inorganic mercury by microorganisms in the environment. The main forms of mercury exposure in the general population are methylmercury (MeHg) from seafood, inorganic mercury (I-Hg) from food, and mercury vapor (Hg^0) from dental amalgam restorations. Often, the different mercury forms determine the route of exposure, absorption, distribution, and target organ toxicity. Hence, a thorough understanding of mercury based on the various chemical forms is critical to studying mercury toxicity and developing an effective and efficient means to control mercury intoxication[49].

1.3.2. Inorganic Mercury Compounds

Approximately 7% to 15% of doses of inorganic mercury compounds are absorbed in the gastrointestinal tract after ingestion. Dermal absorption of inorganic mercury salts is likely, based on the clinical case of mercury intoxication reported following dermal application of ointments containing inorganic mercury salts. Chan. suggested that inorganic mercury may be absorbed through the skin by the transport of mercury across the epidermis and via the sweat glands, sebaceous glands, and hair follicles. Mercury salts are usually non-volatile solids, so poisoning by inhalation is rare. Mercurous chloride is probably slowly absorbed due to its relatively low solubility compared to mercuric chloride[50]. The tissue distribution of mercurous and mercuric mercury compounds appears quite similar.

With chronic exposure to mercury vapor, the notable target organs of toxic effects are the central nervous system and the kidneys. The major clinical features of chronic mercury poisoning from mercury vapor inhalation have been identified in occupational histories as a triad of tremors, psychological disturbances or erethism, and gingivitis[51]. Tremor is considered to be the early neurological sign of poisoning by elemental mercury, which presents intentional tremor or resting tremor, or both. Erethism is a form of toxic organic psychosis characterized by excessive timidity, diffidence, increasing shyness, morbid irritability, mental hyperactivity, and outbursts of temper, along with memory impairment, difficulty in concentration, depression, and somnolence. Gingivitis, stomatitis, and excessive salivation are also associated with high occupational exposure. Proteinuria is the most common sign of the kidney effects due to tubular damage, and nephrotic syndrome can occur in severe cases. In addition, peripheral nerve abnormality can present but is not common. However, workers exposed to mercury vapor may have abnormalities in sensory and peripheral nerve conduction. Elemental mercury vapor may affect the human immune system and can result in a decreased resistance to infection, cancers, or immune dysregulation that can induce the development of allergy or autoimmunity[52].

1.3.3. Lead (Pb)

Lead (Pb) is a naturally occurring metal and generally form lead compounds by combining with two or more elements. Lead reacts with air and water to form lead sulfate, lead carbonates or lead oxide. These compounds act as a protective barrier to prevent corrosion. Lead can also interact with both acid as well as base. It has a low melting point and located above hydrogen in the electromotive series. Although the existence of lead is indicated in nature but human activities has been found as the main reason for increasing lead content in the environment. Lead is released in air from mining of lead, factories utilizing lead compounds, alloys, vehicle exhaust and burning of fossil fuels [53]. The lead is removed from atmosphere by rain and transferred to soil or comes in contact with surface water. Moreover, lead is used as pesticide during vegetable and fruit cultivation. Disposal of lead containing waste products, removal of lead based paints from bridges, buildings and damaged battery from industries further results into the accumulation of lead in municipal landfills. Lead combines very strongly with the soil particles and present in the top layer of soil, Lead enters water bodies or lakes when these soil particles are washed away by rain water. Thus, lead is transferred to animals and plants from air, water, soil and this cycle continues.

Lead is not a foreign material to the human body as it is distributed to the brain, liver, kidney, and bones and is stored in bones and teeth, However, this is only 10 μg/dL in adults and 1.4 μg/dL in children [54]. The guideline value of lead indicated by world health organization is 0.01 mg/L.The Nervous system is mainly affected by lead. The normal functioning of nervous system is influenced if an individual is exposed to lead for a long time. Moreover, longer exposure also causes severe effects on kidney as well as brain. Lead is easily absorbed by the body. Children absorb higher amounts of lead than adults which is highly dangerous as they are developing. In children lead is not absorbed by the bones like in the case of adults therefore they are at a higher risk of poisoning as the other soft tissues absorb the excess lead. Lead acts as a calcium analog, thus it is easily absorbed in people with calcium, zinc, and iron deficiencies. Lead affects the reproductive systems of both males and females[55]. In the case of males, there is a reduction in sperm count and volume, the motility and the morphology of the sperm are also affected.In females who have high exposure to this metal, miscarriage, premature birth, low birth weight, and developmental problems are seen. When toxicity of lead has reached higher amounts, spontaneous abortion of the fetus occurs. Lead can damage cell structure, cell membrane and most importantly it interferes with DNA transcription. At developmental stages, lead passes through the placenta into the body of the fetus. At developmental stages, lead passes through the placenta into the body of the fetus [55].

2. Lead intake by humans

Pb is an environmental pollutant. Despite the low amounts absorbed, prolonged exposure to Pb can accumulate in the human body system, resulting in lead poisoning or toxicity. Lead has a half-life of around 30 days in the blood, after which it diffuses into soft tissues such as the kidneys, brain, and liver and then distributed to bones, teeth and hair as

lead phosphate . ROS (Reactive oxygen species) such as hydroperoxide, hydrogen peroxide, and singlet oxygen are produced as a result of lead poisoning. Pb generates these free radicals which leads to oxidative stress causing cellular damage to the body cells[54]. The body suffers oxidative stress when there is an imbalance of ROS and antioxidant defences. Oxidative stress causes cell and tissue destruction, which increases the likelihood of adverse health outcomes like cardiovascular disease and cancer.

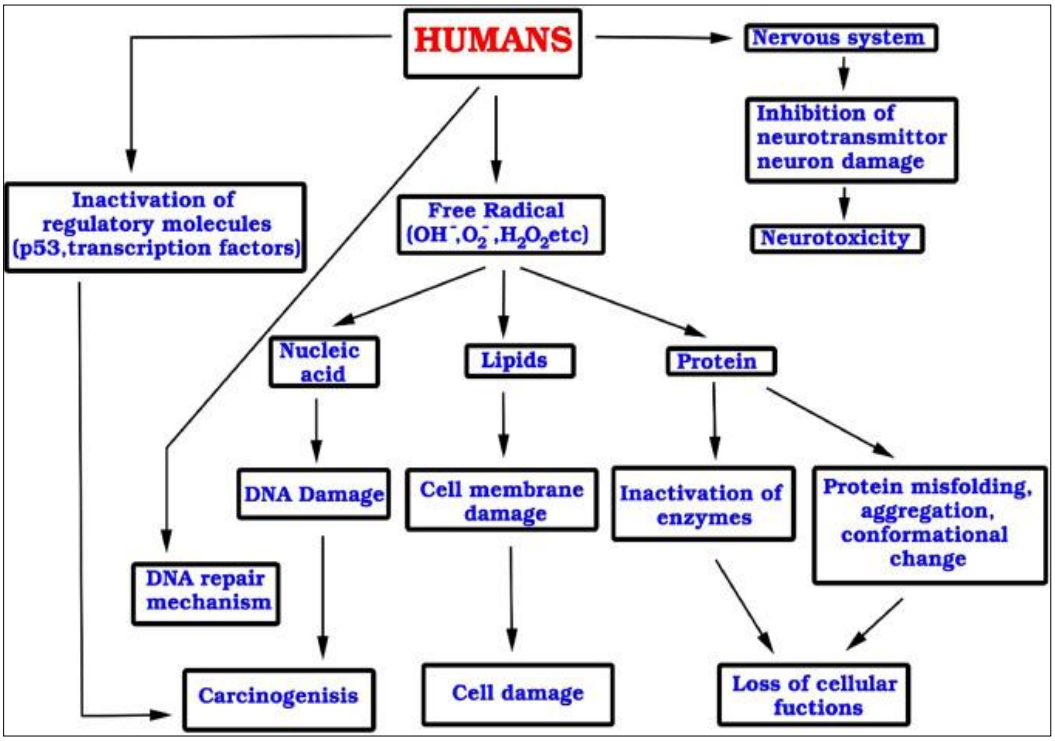

Figure 6 Effects of heavy metal accumulation in human body.

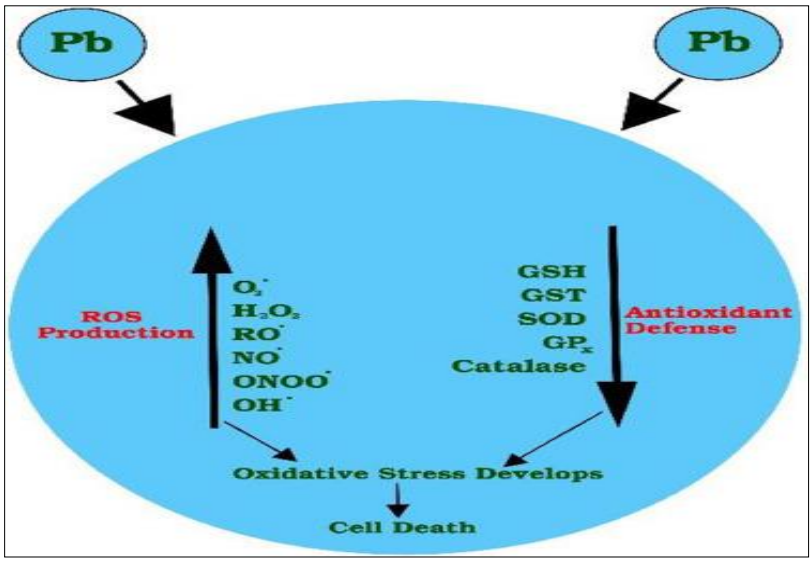

Figure 7 The mechanism underlying the development of oxidative stress in a cell on lead exposure.

The Fig. 1 shows the effect of Pb accumulation in the human body. Increased oxidative stress causes lipid peroxidation, which damages cell membranes resulting in cell damage. Lead inhibits the activity of 5-aminolevulinic acid dehydratase, resulting in hemoglobin oxidation and lipid peroxidation, which can cause red cell hemolysis. displays that when there

is increase in concentration of Pb, the equilibrium between the ROS and antioxidants is altered[56]. The rise in ROS production causes depletion of antioxidant defense causing oxidative stress which eventually leads to cell damage. Lead also interferes with the activity of other antioxidant enzymes including superoxide dismutase and catalase. Glutathione in the body helps to maintain ROS in balance. Ninety percent of glutathione in the cell is reduced, while ten percent is oxidized, and it serves as an antioxidant defense mechanism. Glutathione stabilizes ROS and is reduced back to GSH by glutathione reductase after being oxidized to glutathione disulfide. By attaching to the sulfhydryl group of glutathione, Pb inactivates it, making GSH replenishment ineffective and increasing oxidative stress. The deposition of a small amount of Pb in the human body causes cellular malfunction and has a negative impact on an individual's health[57]

2.1. Physiological and biochemical effects of lead accumulation in human beings

Lead (Pb) is one of the ancient heavy metals used by human beings. From time immemorial, Pb has huge applications in the manufacturing of instruments and tools due to its splendid physical and chemical properties. Lead is used in the manufacture of boats, bearings, buildings, paints, lead batteries, automobiles, gasoline, pipes, ceramics, plastics, and in smelting, mining processes, and the arms industry. Studies have revealed that both adults and children are affected by lead toxicity. In the case of children, both internal and external tissues are soft, hence making them more susceptible. Its malleability, ductility, corrosion resistance, low melting point, and abundant availability are the reasons lead is used till today, even though its accumulation is hazardous. Being non-biodegradable in nature, the removal of lead from the environment is inevitable[58]. Lead toxicity and lead accumulation in humans is one of the major health concerns. While occupational causes like dermal contact and inhalation contribute to the indirect intake of lead in humans, consumption of Pb contaminated food and water are direct sources of accumulation. Acute Pb toxicity leads to dysfunction of the kidney, reproductive system, and brain while chronic damages are caused to the CNS and PNS.

Lead also inhibits the synthesis of hemoglobin. Pregnant women with low calcium, iron or zinc levels are prone to the effects of lead accumulation. Lead is a poisonous metal and disturbs the functions of almost every organ in the human body as depicted in Fig. 3. Common symptoms observed are behavioral changes, lowered IQ, slow learning in children, diarrhea, anemia, skin allergies, kidney malfunctioning and many more. Also the Pb interacts with mechanisms and functions of the male reproductive system and affects the sperm count. Even low levels of Pb in the kidney cause chronic renal malfunctioning. It is found that Pb interferes with the activities of several enzymes, delta-aminolevulinicacid dehydratase (ALAD), ferrochetase catalase, superoxide dismutase (SOD) and many more. Lead-induced oxidative stress increases radical production damaging the cell membranes, cell functions and DNA[59].

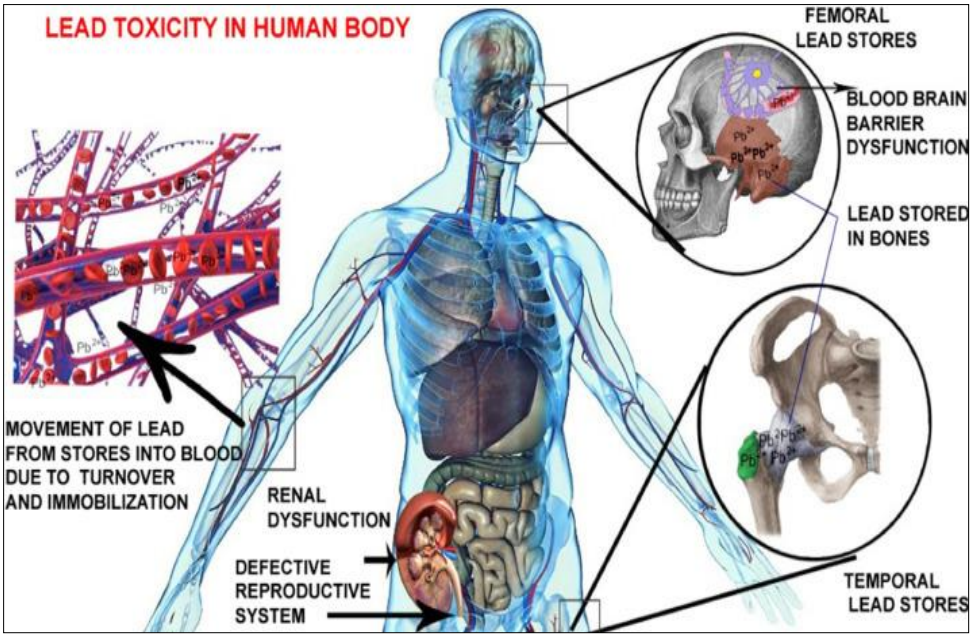

Figure 8 Diagrammatic representation of lead accumulation in the major organs

2.1.1. Nickel

Nickel occurs in the Earth's crust to about 0.01% mainly as sulfide, oxide and silicate minerals. Natural geological activities such as weathering and volcanoes led to a nickel distribution in natural environments at modest levels. Metallic nickel and nickel compounds are used in manifold industrial and commercial applications such as stainless steel and other nickel alloys, electroplating, foundries, catalysts, batteries, electronics, ceramics, pigments, and coinage. The related industrial processes (e.g. mining, milling, melting and other metallurgical processes) and also the combustion of fossil fuels result in anthropogenic nickel emission into the environment, mainly in the ambient air and aquatic systems. Airborne nickel-bearing particles are deposited to surface water and soil and thus nickel can be accumulated by plants and animals[60].

The main exposure route for nickel in the general population is food with an average daily nickel intake of about 0.1–0.3 mg. In contrast, nickel uptake by inhalation is below 0.0008 mg day^{-1} for non-smoking urban residents. Smoking tobacco contributes up to 0.023 mg daily nickel uptake (40 cigarettes a day). Another exposure route is skin contact with stainless steel, jewelry and coins.

Workers in the nickel producing and processing industry are occupationally likely higher exposed than the general population and their main exposure pathway is inhalation and, to a lesser extent, dermal contact.

Nickel bioavailability to organisms and related biochemical processes are strongly dependent on the chemical and physical form (species) of the element. This requires nickel speciation analysis for a deeper comprehension of nickel toxicological effects in organisms[61]

2.1.2. Techniques to detect trace element

Recently trace elements content of food and tissues has been created interest among research scholars. Such determinations required sensitivity and accurate methods of analysis. Most of the trace elements are estimated with a help of colorimetric and spectrographic methods of analysis. Atomic absorption spectrometry-based on flames arcs and sparks (flame by electrothermal)[62]:

- Emission spectroscopic methods.
- Neutron activation analysis.
- Electrochemical methods.
- Isotope dilution mass spectrometry.
- Atomic X-ray fluorescence spectroscopy.

3. Emission spectroscopic methods

Emission spectroscopy is a method of chemical analysis that uses the intensity of light emitted from a flame, plasma, arc, or spark at a particular wavelength to determine the quantity of an element in a sample. The wavelength of the atomic spectral line in the emission spectrum gives the identity of the element while the intensity of the emitted light is proportional to the number of atoms of the element. The sample may be excited by various methods

The contribution of electrochemical methods to the knowledge of dynamic speciation of toxic trace elements is critically reviewed. Due to the importance of dynamic considerations in the interpretation of the electrochemical signal, the principles and recent developments of kinetic features in the interconversion of metal complex species will be presented[63]. As dynamic electrochemical methods, only stripping techniques (anodic stripping voltammetry and stripping chronopotentiometry) will be used because they are the most important for the determination of trace elements. Competitive ligand exchange-adsorptive cathodic stripping voltammetry, which should be considered an equilibrium technique rather than a dynamic method, will be also discussed because the complexing parameters may be affected by some kinetic limitations if equilibrium before analysis is not attained and/or the flux of the adsorbed complex is influenced by the ability of the natural complexes in the sample. For a correct data interpretation and system characterization the comparison of results obtained from different techniques seems essential in the articulation of a serious discussion of their meaning[64].

3.1. Atomic X-ray fluorescence spectroscopy

Sampling of animal and human tissues have been discussed in many papers. Two types of sampling are used in experiments with animals and humans. In the first type the investigator uses experimental animals which can be

sacrificed as necessary and dissected to produce whatever specific tissues are desired Here replication of animals is common, total weight of samples is not limiting, and the analyst is generally present during the sampling. The major decisions involve selection of the specific tissue that will, on analysis, yield the most important data. In the second type of experiment the animal or person being investigated must remain alive and experience minimum discomfort. Here the number of individuals is usually limited, and the analyst receives the samples from a nurse, technician, or other person who is generally not a part of the research team[65]. In these instances, blood or serum, urine, hair, and perhaps needle biopsy materials are the tissues that are generally available. In this type of sampling, decisions include the kind of tissue or tissues most useful in characterizing the status of the subject with respect to the element in question and whether the data on environment, diet, health or disease, water supply, etc., are adequate for the purposes of the experiment. Very frequently the investigator is forced to use less than adequate samples rather than do nothing.

Another decision in sampling under these conditions concerns contamination of samples during sampling[66]. Blood samples drawn with stainless-steel needles may be unsatisfactory for chromium, and those drawn through rubber tubing may be unsatisfactory for zinc. Plastic urine containers may irreversibly absorb heavy metals. It would be useful for some central organization to sponsor the production and distribution of syringes, blood needles, and containers for blood and urine that would be suited to trace element studies on samples obtained from humans and domestic animals. A second desirable, but perhaps unattainable, feature would be the establishment of a uniform terminology suited to coding, for describing the environment, health and disease, diet, etc., of the subject sampled [66, 67]

4. Conclusion

In closing, as we view the importance of trace elements in living organisms, detailed studies indicate a fine balance must be obtained in trace elements concentration in order to secure health and even to maintain life in living organisms. However, danger of over dose, most elements in excess of certain limits of concentration have toxic effects. Trace elements may also act against each other, and in a few cases one may assist another. It is, however, most exceptional for one to be able to replace another. Analysis of daily intake: not practical, large variance (many elements) Checking for alleviation of symptoms following replenishmen: most reliable method of diagnosing deficiency (many elements), there are few methods that allow accurate diagnosis, especially in cases with mild to moderate deficiency. The development of more accurate methods is an issue that must be addressed in future.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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