Review Article

Trace Elements in Human Nutrition (II) – An Update

Aliasgharpour Mehri

Department of Biochemistry, Reference Health Laboratory, Ministry of Health and Medical Education, Tehran, Iran

Abstract

The dietary requirement for an essential trace element is an intake level which meets a specified criterion for adequacy and thereby minimizes risk of nutrient deficiency or excess. Disturbances in trace element homeostasis may result in the development of pathologic states and diseases. This article is an update of a review article "Trace Elements in Human Nutrition-A Review" previously published in 2013. The previous review was updated to emphasis in detail the importance of known trace elements so far in humans' physiology and nutrition and also to implement the detailed information for practical and effective management of trace elements' status in clinical diagnosis and health care situations. Although various classifications for trace elements have been proposed and may be controversial, this review will use World Health Organization(WHO) classification as previously done. For this review a traditional integrated review format was chosen and many recent medical and scientific literatures for the new findings on bioavailability, functions, and state of excess/deficiency of trace elements were assessed. The results indicated that for the known essential elements, essentiality and toxicity are unrelated and toxicity is a matter of dose or exposure. Little is known about the essentiality of some of the probably essential elements. In regard to toxic heavy metals, a toxic element may nevertheless be essential. In addition, the early pathological manifestations of trace elements deficiency or excess are difficult to detect until more specific pathologically relevant indicators become available. Discoveries and many refinements in the development of new techniques and continual improvement in laboratory methods have enabled researchers to detect the early pathological consequences of deficiency or excess of trace elements. They all are promises to fulfill the gaps in the present and future research and clinical diagnosis of trace elements deficiencies or intoxications. However, further investigations are needed to complete the important gaps in our knowledge on trace elements, especially probably essential trace elements' role in health and disease status.

Keywords: *Biological bioavailability, deficiency diseases, nutritional essentiality classification, toxic heavy metals, trace and ultra-trace elements*

Background

There are two faces about trace elements: They are beneficial and/or toxic. Minerals form only 5% of the typical human diet but are essential for normal health and function. For the known essential elements, essentiality and toxicity are unrelated and toxicity is a matter of dose or exposure. In the past years, considerable research has been carried out to better understand the physiological role and the health consequences of trace elements. This article is an update of a review article "Trace elements in human nutrition: A review" previously published in 2013.[1] The previous review was updated to emphasis in detail the importance of known trace elements so far in humans' physiology and nutrition and also to implement the detailed information for practical and effective management of trace elements' status in clinical diagnosis and healthcare situations. For this review (Materials and Methods), a traditional integrated review format was chosen, and many recent medical and scientific literatures for the new findings on bioavailability, functions, and state of excess/deficiency of trace elements were assessed and of trace elements were assessed and related articles were studied. Although various classifications[2] for trace elements have been proposed and may be controversial, this review will use World Health Organization (WHO) classification as previously done: *essential elements, probably essential elements, and potentially toxic elements.* This classification includes 19 elements that are based on the nutritional significance.[3] Within each of these groups, elements for which there is clear evidence that either deficiency or excess causes

How to cite this article: Mehri A. Trace elements in human nutrition (II) – An update. Int J Prev Med 2020;11:2.

Address for correspondence:
Dr. Aliasgharpour Mehri, Department of Biochemistry, Reference Health Laboratory, Ministry of Health and Medical Education, Tehran, Iran.
E-mail: mehri9@gmail.com

Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.IJPVM_48_19

Quick Response Code:

significant health problem are considered first. Trace elements (or trace minerals) are usually defined as minerals that are required in amounts between 1 and 100 mg/day by adults or make up less than 0/01% of the total body weight.[1-3] Ultra-trace minerals generally are defined as minerals that are required in amounts less than 0/001 mg/day.[3]

Essential elements

Chromium

Chromium (Cr) as an essential nutrient (glucose tolerance factor) potentiates insulin, and thus influences carbohydrate, lipid, and protein metabolism. However, the nature of the relationship between chromium and insulin function has not been defined.[3] In addition, the results of investigations indicated that chromium supplementation did not appear to ameliorate insulin resistance or impaired glucose metabolism, and thus is unlikely to attenuate diabetes risk.[4,5] The mechanism of absorption of chromium from intestine has not been clearly identified, but it apparently involves processes other than simple diffusion. It has been claimed that many factors such as oxalate, iron, and high dietary intakes of simple carbohydrates change the bioavailability or absorption of chromium.[6,7] In addition, it has been found that chromium absorption is elevated by chemically induced diabetes and depressed by aging.[8] The adequate intake of chromium for adults is 20–35 μg/day.[9] Chromium deficiency is generally limited to hospitalized patients with increased catabolism and metabolic demands in the setting of malnutrition. Some of the first case reports of chromium deficiency were from patients receiving parenteral nutrition.[10] Studies have indicated that in diabetic patients receiving chronic total parenteral nutrition, human chromium deficiency has been associated with increased insulin requirements.[10,11] Chromium supplementation in these patients improved glucose tolerance. Thus, an abnormal glucose tolerance may indicate a low chromium status, and an improvement in glucose tolerance after chromium supplementation may be a valid indicator of chromium deficiency. Chromium is a transition element and exists in multiple ionic states. Dietary chromium is in the trivalent state. Depending on the route of exposure (e.g., oral, dermal, or inhalation) and chromium significant chemical forms, the effect related to a given dose would be different. Trivalent chromium has low toxicity that deleterious effects of excessive intake of this form of chromium do not readily occur and there are no reports of adverse effects of dietary chromium (trivalent chromium).[5] However, airborne hexavalent chromium (VI) toxicity has been established as a work-related etiology of lung cancer in stainless steelworkers.[5,12,13] Oral administration of 50 μg/g diet has been found to induce growth depression together with liver and kidney damage in experimental animals.[14] Apart from acute intoxication, chromium toxicity through oral ingestion is apparently not of practical importance for humans.

Copper

Copper (Cu) in biological systems may be present in both +1 and +2 valance states. Thus, its major function involves oxidation–reduction reactions. It is an integral component of many enzymes, including ceruloplasmin (copper transporter and ferroxidase), cytochrome c oxidase (electron transport), zinc-copper superoxide dismutase (antioxidant defense), dopamine-mono-oxygenase (neurotransmitter synthesis), lysyl oxidase (collagen cross-linking, bone formation), dopamine beta-hydrolase (skin pigmentation), and tyrosinase (melanin production).[15,16] Several constituents occurring naturally in food have been found to affect the absorption of copper from the intestine and to increase or decrease its bioavailability. Apart from a low intake of dietary copper, which appears to increase the efficiency of copper absorption,[17,18] the other main dietary factor which enhances the bioavailability of copper appears to be a high level of protein intake.[19] Absorption occurs by active transport process at lower levels of dietary copper and by passive diffusion at high levels of dietary copper. Absorbed copper is loosely bound to plasma albumin and amino acids in the blood and taken to the liver and is incorporated into the copper-containing protein ceruloplasmin, which serves to transport copper from the liver to peripheral tissues.[20,21] Furthermore, ceruloplasmin has an independent role in iron metabolism, in which it serves as a plasma ferroxidase, converting iron to a valence that can be bound by plasma transferring.[20,21] Copper deficiency or hypocupremia is defined as a serum copper level of 0.8 μg/mL or less (normal serum Cu 0.64–1.56 μg/mL). About 93% of serum copper is normally bound to ceruloplasmin and is usually accompanied by hypoceruloplasmin[22] (normal serum ceruloplasmin 0.18–0.40 μg/mL). Hypercupremia occurs naturally during pregnancy and is associated with the so-called "acute phase" reaction of a number of diseased states. It is almost always accompanied by hyperceruloplasmin.[22] Extreme form of copper deficiency is Menkes disease, also known as Menkes kinky (steely) hair syndrome, a congenital x-linked genetic disorder with an incidence of about 1:100,000 live births.[23,24] The formation of steely hair is attributed to the loss of copper catalyzed disulfide bond formation. Menkes disease is caused by a mutation of the transport protein mediating copper uptake from the intestine, encoded by the ATP7A gene. Inactivating mutations in this gene result in severe copper deficiency with progressive neurologic deterioration and death during early childhood.[23] This gene is closely related to the gene responsible for copper overload in Wilson's disease. Intravenous administration of copper may help raise plasma copper concentrations; however, urinary copper excretion increases accordingly, and the course of vascular and cerebral degeneration is irreversible. Red cell copper is not decreased and neutropenia and anemia in Menkes disease do not appear.[25] Wilson's disease is characterized by excessive copper accumulation and is caused by a mutation

in a copper-ATPase enzyme that prevents the incorporation of copper into ceruloplasmin.[26] It is an autosomal recessive disorder with a frequency of 1:30,000 to 1:100,000 live births. Copper deposition occurs in hepatic parenchymal cells, brain, periphery of the iris, and kidneys.[27,28] The age of onset and form of presentation are very variable. Wilson's disease can be controlled, and in some cases halted by early and persistent treatment with zinc acetate or copper chelators, such as penicillamine. Zinc competes with copper for absorption in the gastrointestinal tract. Furthermore, copper toxicity may occur subsequent to ingestion of copper-contaminated solutions, the use of copper-containing intrauterine devices, the use of copper salts in animal feeds, and exposure to copper-containing fungicides.[25]

Zinc

Most biochemical roles of zinc (Zn) reflect its involvement in a large number of enzymes or as a stabilizer of the molecular structure of subcellular constituents and membranes. Zinc participates in the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids.[3,29] It has recently been shown to play an essential role in polynucleotide transcription and translation, and thus in the processes of genetic expression. Its involvement in such fundamental activities probably accounts for the essentiality of zinc for all forms of life.[3,30,31] Zinc plays an important role in cell proliferation, differentiation, and metabolic activity of the cell as well.[32] In addition, it supports normal growth and development during pregnancy, childhood, and adolescence.[33] Several studies have suggested a benefit of zinc supplementation in children with acute diarrhea in resource-limited countries.[34,35] Zinc absorption is concentration-dependent and occurs throughout the small intestine. Under normal physiological conditions, the transport processes of uptake are not saturated.[36] Absorption is inhibited by the presence of phytates and fiber in the diet that bind to zinc, as well as dietary iron and cadmium.[37] Mild zinc deficiency appears to be common, especially in resource-limited countries because the diet is relatively low in zinc.[37] A reduced growth rate and impaired resistance to infection are frequently the only manifestation of mild deficiency in human.[38] The genetic disorder related to zinc metabolism is acrodermatitis enteropathica (AE), which is an autosomal recessive disease and there is an inability in zinc absorption.[38,39] AE is characterized by signs and symptoms of severe zinc deficiency including diarrhea, poor growth, and poor immune function. Humans are very tolerant to high zinc intakes up to 100 mg/day.[40] However, high zinc intake from contaminated food or beverages and acute zinc poisoning has been associated with nonspecific gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, and vomiting.[41,42] Long-term exposure to high zinc intakes have been shown to interfere with the metabolism of other trace elements such as copper absorption.[43,44] Furthermore, both type 1 and type 2 diabetics can exhibit hyperzincuria, which may have a role in the immune dysfunction associated with diabetes mellitus.[45] Zinc supplementation in diabetic patients may improve immune function and also increases the HbA1c levels and leads to worsening glucose intolerance.[46]

Selenium

Selenium (Se) is an essential trace element in humans and animals with high metabolic activity. Its main functions in humans are the antioxidant defense activity of glutathione peroxidase as a selenoprotein in the regulation of immunity, thyroid function, and reproductive system. Selenium is part of the active site of glutathione peroxidase (GSH-Px), an antioxidant enzyme.[47,48] Adequate level of dietary selenium intake and optimal selenoprotein expression guarantees protection from free-radical oxidation, which is observed in neurodegenerative, cardiovascular, thyroid disease, and some forms of cancer.[49] The optimal daily intake is 20–70 μg/day, and the toxic level is 5 mg/day. Its half-life in the body is 50–60 days.[50,51] Selenium is present in foods mainly as the amino acids selenomethionine and selenocysteine. Around 80% of dietary selenium is usually absorbed, but the amount is affected by chemical form in the diet and a range of other factors including intake of protein and the presence of any considerable levels of toxic elements in the diet, such as mercury and arsenic. The absorption of selenomethionine occurs through active transport.[52] Selenium, in the form of selenocysteine, is incorporated into selenoproteins structure.[53] The best known of these enzymes is glutathione peroxidase, which plays an important role in protecting cell membranes from damage by free radicals.[47,48] The highest concentrations of selenium are observed in liver, kidneys, pancreas, skeletal muscle, thyroid gland, and myocardium. Selenium content is decreased with aging, smoking, inflammation, and some types of cancer.[54] Selenium deficiency leads to impairment of both innate and adapted immunity.[55] Persons with insufficient selenium intake are characterized by impaired antiviral defense, immune response, and increased risk of autoimmunity.[56] In particular, selenium deficiency is associated with the development of systemic connective tissue diseases such as sclerodermia, lupus, rheumatoid arthritis, and raynaud's syndrome.[57] Moreover, a significant relationship between selenium deficiency and allergic reactions and infective allergic asthma was demonstrated.[58] In addition, at selenium deficiency, there is an increased accumulation of arsenic, cadmium, and mercury in the body. Selenium is an antagonist of mercury and arsenic and it is able to protect the body against cadmium, lead, thallium, and silver.[50] Although the biochemical mechanism of selenium toxicity has not been clearly established,[47,59] selenium can have toxic effects at high doses. Its toxicity occurs with excess dietary intake, either through diets naturally high in selenium or "mega dose" supplementation. Chronic selenium poisoning in people is

defined as hair loss, nail discoloration or brittleness, or two or more of the following symptoms: muscle or joint pains, headache, foul breath, fatigue/weakness, gastrointestinal symptoms, or cutaneous eruption.[51,60] There are many hypothesis suggested by different studies regarding selenium deficiency/toxicity; however, hypothesis that relates with the deficiency of selenium is the most accepted hypothesis.[51]

Molybdenum

Molybdenum (Mo) is a trace element essential for micro-organisms, plants, and animals. Initially, mistaken for lead, molybdenum was named after the Greek word molybdos, meaning lead-like. In humans, only four enzymes requiring molybdenum have been identified to date: sulfite oxidase, xanthine oxidoreductase, aldehyde oxidase, and mitochondrial amidoxime-reducing component (mARC).[61] Xanthine oxidoreductase is present in two forms: xanthine dehydrogenase (XDH) and xanthine oxidase (XO). Molybdenum takes part in the active site of these enzymes and functions as an enzymatic cofactor.[62] In addition, it plays a role in the detoxification of the organism and production of important intermediary products. A total of 59%–94% of dietary molybdenum is absorbed in the gastrointestinal tract depending on the ingested dose.[63] In humans, molybdenum deficiency is rather rare and is associated with impaired reproductive functions and growth retardation.[64] Molybdenum deficiency is accompanied by decreased blood and urinary uric acid concentration, and increased xanthine and hypoxanthine excretion.[64] High amounts of molybdenum are toxic. Increased XDH activity results in accumulation of uric acid, gout development, and reactive oxygen species (ROS)-related diseases.[65] Increased XDH activity and hyperuricemia are observed in ischemia, cardiovascular diseases, metabolic syndrome, and diabetes complications.[66]

Iodine

Iodine (I) is an essential constituent of the thyroid hormone triiodothyronine (T3) and thyroxine (T4) with plasma half-lives of approximately 2 and 8 days, respectively.[67] Iodine from the diet is absorbed throughout the gastrointestinal tract. Dietary iodine is converted into the iodide ion before it is absorbed. The iodide ion is 100% bioavailable and absorbed totally from food and water. This is, however, not true for the iodine within thyroid hormones ingested for therapeutic purposes. In the circulation it is taken up by the thyroid gland and any excess amount is filtered by the kidneys and excreted. All biological actions of iodide are attributed to the thyroid hormones. The physiological actions of thyroid hormones can be categorized as (1) growth and development and (2) control of metabolic processes in the body. Thyroid hormones play a major role in the growth and development of the brain and central nervous system in humans from the 15th week of gestation to 3 years of age.[68] If iodine deficiency exists during this period and results in thyroid hormone deficiency, the consequence is derangement in the development of the brain and central nervous system.[69] The other physiological role of thyroid hormones is to control several metabolic processes in the body. These include carbohydrate, fat, protein, vitamin, and mineral metabolism. For example, thyroid hormone increases energy production, increases lipolysis, and regulates neoglucogenesis and glycolysis.[69] In addition, it has been suggested that the effective utilization of iodine depends on a selenium-containing enzyme, and thus on an adequate selenium status.[70] Selenium is a necessary component of the deiodinase enzyme that removes iodine molecules from T4 converting it into T3. When patients suffering from various forms of thyroid disease were tested for selenium levels, all were found to be lower than normal healthy people.[70] The risk of thyroid diseases depends on iodine intake and is characterized by the U-shaped curve where both excess and deficiency exert a negative effect.[71] Iodine deficiency is associated with goiter, hypothyroidism, increased risk of miscarriage, preterm birth, congenital fetal abnormalities, and elevated incidence of neonatal death.[72-74] In hypothyreosis, the development of decreased blood sodium is observed.[75] One should not simultaneously take supplements containing iodine and lithium carbonate. Lithium reduces the activity of thyroid gland, while iodine enhances the manifestation of lithium side effects.[76] Thyrotoxic states are observed in Graves' disease, autonomous toxic adenoma. Most frequently these diseases are associated with thyrotropin receptor mutation and G-protein α-subunit stimulation.[77] Moreover, the development of benignant and malignant tumors in the thyroid gland in women occurs more frequently when compared with men.[78] The key facts on essential trace elements are summarized in Table 1.

Probably essential elements

Manganese

Manganese (Mn) is an essential element in the human body that is mainly obtained from food and water. Manganese is absorbed through the gastrointestinal tract and then transported to organs enriched in mitochondria (in particular the liver, pancreas, and pituitary) where it is rapidly concentrated.[79] Excretion of manganese is primarily through bile into the gastrointestinal tract. Manganese acts as an activator of many enzymes and as a component of metalloenzymes such as manganese superoxide dismutase (MnSOD) that is mainly responsible for scavenging ROS in mitochondrial oxidative stress. In addition, it is involved in the glucose and lipids' metabolism, acceleration of protein synthesis, vitamin C, and vitamin B, catalysis of hematopoiesis, regulation of the endocrine, bone and tissue formation, skeletal growth, reproduction, and immune function improvement.[79] Both deficiency and intoxication are associated with adverse metabolic[80] and neuropsychiatric

Table 1: Key facts on essential trace elements

Element	Key facts	Bioavailability	Deficiency	Toxicity
Cr	Influences carbohydrate, lipid, and protein metabolism by potentiating insulin.	The mechanism of absorption of Cr from intestine has not been clearly identified. It involves processes other than simple diffusion and many factors change the bioavailability or absorption of Cr.	Limited to hospitalized patients with increased catabolism and metabolic demands in the setting of malnutrition.	Airborne hexavalent chromium (VI) toxicity has been established as a work-related etiology of lung cancer in stainless steel workers.
Cu	Major function involves oxidation-reduction reactions. It is an integral component of many enzymes.	Cu absorption occurs by active transport at lower levels of dietary copper and by passive diffusion at high levels of dietary copper. Absorbed copper is loosely bound to plasma albumin and amino acids in the blood and in the liver is incorporated into the copper-containing protein ceruloplasmin.	Extreme form of copper deficiency is Menkes disease, or Menkes kinky (steely) hair syndrome.	Toxicity may occur subsequent to ingestion of copper-contaminated solutions, use of copper-containing intrauterine devices, use of copper salts in animal feeds, and exposure to copper-containing fungicides. Wilson's disease, autosomal recessive disorder, is excessive copper accumulation. Disorder that is caused by a mutation in a copper-ATPase enzyme and prevents the incorporation of copper into ceruloplasmin.
Zn	Zn involves in a large number of enzymes or is a stabilizer of the molecular structure of subcellular constituents and membranes. It plays an important role in cell proliferation, differentiation, and metabolic activity of the cell and supports normal growth and development. Also, it plays an essential role in the processes of genetic expression.	Zn absorption is concentration dependent and occurs throughout the small intestine. It is inhibited by the presence of phytates and fiber in the diet that bind to zinc, as well as dietary iron and cadmium.	Genetic disorder related with zinc metabolism is acrodermatitis enteropathica.	High Zn intake interferes with the metabolism of other trace elements such as copper absorption.
Se	Se has antioxidant defense activity of glutathione peroxidase as a selenoprotein in regulation of immunity, thyroid function, and reproductive system. Se is present in foods mainly as the amino acids selenomethionine and selenocysteine. Se content decreases with age, smoking, inflammation, and some types of cancer.	About 80% of dietary Se is absorbed but the amount is affected by chemical form in the diet and other factors including intake of protein and the presence of any levels of toxic elements in the diet, such as mercury and arsenic.	Se deficiency is associated with the development of systemic connective tissue diseases such as sclerodermia, lupus, rheumatoid arthritis, and Raynaud's syndrome. At Se deficiency, there is an increased accumulation of arsenic, cadmium, and mercury in the body.	Se can have toxic effects at higher doses, although the biochemical mechanism of its toxicity has not been established.
Mo	Functions as an enzymatic cofactor.	Total of 59%-94% of dietary Mo is absorbed in GI tract depending on the ingested dose.	Mo deficiency is rare and is associated with impaired reproductive functions and growth retardation.	High amounts of Mo are toxic.
I	It is an essential constitute of the thyroid hormone triiodothyronine (T3) and thyroxine (T4). Dietary iodine is converted into iodide ion before it is absorbed.	I ion is 100% bioavailable and absorbed totally from food and water.	I deficiency is associated with goiter, hypothyroidism, increased risk of miscarriage, preterm birth, congenital fetal abnormalities, and elevated incidence of neonatal death.	Thyrotoxic states are observed in Graves' disease, autonomous toxic adenoma.

Cr=C, Cu=Copper, Zn=Zinc, Se=Selenium, Mo=Molybdenum, I=Iodine, GI=Gastrointestinal tract

effects. Manganese deficiency in humans is very unusual, but has been reported in individuals on a highly restricted diet. In experimental studies in humans, manganese deprivation was associated with scaly dermatitis and dyslipidemia.[81] Environmental or occupational manganese overexposure in at-risk populations such as miners, welders, and steel makers is toxic. Manganese ore mining and its processing cause air and water pollution, threatening the health of workers and general populations residing near factories through oral ingestion, inhalation, and dermal contact.[82] Furthermore, excessive exposure to manganese may cause Parkinsonian-like motor and tremor symptoms and adverse cognitive effects, including problems with executive functioning, resembling those found in later-stage Parkinson's disease.[83] Furthermore, it is known that homeostasis of iron and manganese is tightly interrelated. In particular, manganese possesses a high affinity to transferrin receptors even in comparison to iron (III). Ferroportin is also considered to be a possible manganese transporter.[84,85]

Silicon

Silicon (Si) is a beneficial trace element that is widely distributed in foods with several dietary sources of grains, root vegetables, bean, corn, fruits, dried fruits, nuts, and also drinking water. Various alcoholic beverages also contain considerable amounts of silicon. Silicon compounds from food in the presence of hydrochloric acid and other gastric acids in the gastrointestinal tract are hydrolyzed into bioavailable forms of silicic acid (ortho, meta, di, and tri-silicates)[86] that readily diffuses into the blood circulation where it is distributed and accumulated into various tissues and organs such as kidneys, liver, bone, spleen, lungs, skin (collagen synthesis), and connective tissues.[87,88] It also improves the structural integrity of skin, hair, and nails, and bone calcification; modulates the immune system and inflammatory response; accelerates the rate of bone mineralization; and mitigates the risk of atherosclerosis.[89-91] The amount of silicon in tissues decreases with age. Silicon is filtered by the glomerulus because it does not form any bonds with plasma proteins.[87] Hence, about 70%–80% of plasma silicon is eliminated by kidneys within 3–8 h after meal ingestion.[87,92] It has also been suggested that silicon may decrease the bioavailability of aluminium by blocking the uptake of the latter by the gastrointestinal tract and impeding its reabsorption in the kidneys, and thus protecting against the toxic actions of aluminium.[93,94] Silicon levels tend to be higher in foods derived from plants than foods from an animal source. In addition, although there are several potential dietary sources, silicon bioavailability from foods is low. Thus, it may be prudent to increase intake through other innovative means such as biofortification of edible parts of plants.[90,95-97]

Nickel

It is well-accepted that nickel (Ni) is as an essential trace nutrient in plants, animals, and humans. However, less than 10% of nickel ingested with food and drinking water is absorbed by the gastrointestinal tract.[3] Although the biological function of nickel is still somewhat unclear in the human body, however, nickel is found in the body in highest concentrations in the nucleic acids, particularly RNA, and is thought to be somehow involved in protein structure or function. It has been speculated that nickel may play a role, as a cofactor, in the activation of certain enzymes related to the breakdown or utilization of glucose. Nickel may aid in prolactin production, and thus be involved in human breast milk production.[98-101] More research is needed to reveal the properties of this interesting mineral in the human body. Small quantities of nickel are essential for the body, but when the uptake is too high it can be toxic to human health. Studies have shown that humans may be exposed to nickel during breathing air, eating food, or smoking cigarettes and acute exposure of human body to nickel may cause several health problems such as liver, kidney, spleen, brain and tissue damage, vesicular eczema, lung, and nasal cancer.[100,102] In addition, acute toxicity can follow exposure to nickel carbonyl, a gas generated as part of the refining process for the metal.[103] Occupational exposure to nickel and its compounds can also cause allergic dermatitis known as "nickel allergy" in sensitized individuals. Dermatitis due to wearing nickel-plated objects such as jewelry is well-documented.[104,105] Nickel deficiency has not been shown to be a concern in humans; despite this, it may cause biochemical changes, such as reduced iron resorption that leads to anemia. It can disturb the incorporation of calcium into a skeleton and lead to parakeratosis-like damage, which finds expression in disturbed zinc metabolism. It has found that nickel deficiency particularly affects carbohydrate metabolism.[99]

Boron

Boron (B) and its compounds have been known for a while as beneficial for the metabolism of humans and animals. It has important roles in physiological and metabolic activities of microbial and plant systems.[105,106] The essentiality of boron for human has not been reported; instead, it is considered as a probably essential element by the WHO.[3] It is ingested from the diet and absorbed from gastrointestinal tract completely and presented in body as boric acid,[107,108] and then it excreted completely in the urine. Very little is known about its transport in the body. Boron has roles in steroid hormone metabolism, healthy bone development, and cell membrane maintenance.[109,110] It does not tend to accumulate in tissues. However, bone, nails, and hair have been found to have higher boron levels, whereas fat tissue has low boron levels.[111] People consume many products containing boron in their daily life mostly from fruits and vegetables. It exists abundantly in leafy vegetables, fruits, nuts, and legumes.[112-114] When consumed at high doses, it can cause developmental and reproductive abnormalities.[113] There is only limited number of cases

for boron intoxication involving human subjects. Reports suggest that environmental or industrial boron exposure is not a treat for human health.[115-117] People who work in boron mine plants have a mean blood boron level of 224 ng/g and show no symptoms of toxicity.[117] Oral exposures of humans to high levels of boric acid have resulted in little or no observable toxicity.[118] Chronic exposure to boron causes neurological effects, kidney damage, diarrhea, anorexia, weight loss, and testicular atrophy.[119] Boron deprivation results in impairment of growth, abnormal bone development, decrease in blood steroid hormone levels, and an increase in urinary calcium excretion in humans and animals.[120] In addition, it is found that in animals and humans, boron deficiency is also related to the decrease in the electrical activity of the brain, short-term memory, and decrease in skills in performing tasks, whereas boron supplementation increases brain functions. These effects of boron could be attributed to the changes in membranes providing nerve-impulse transmission by boron.[114,121,122] Boron deficiency is also suggested to be the possible causal agents in Kashin–Beck disease which is a bone disease having a high incidence in China.[123]

Vanadium

Vanadium (V) is widely distributed in all organisms. In humans, the vanadium content in blood plasma is around 200 nM, while in tissues it is around 0.3 mg/kg and mainly found in bones, liver, and kidney.[124,125] The two main routes for absorption of vanadium are breathing and ingestion. The daily dietary intake in Iran is estimated to be 32.6–135 μg/g.[126] Also, vanadium is found in potable water in concentrations around 1 μg/L; thus, its intake by this source depends on the daily ingested volume.[127] Therefore, the typical daily dose consumed by humans corresponds to 10–30 μg of vanadium per day. However, most of the dietary vanadium is usually excreted in the feces, meaning that the vanadium accumulation in the body does not constitute a potential hazard.[128-131] Toxic effects usually occur only as the result of industrial exposure to high levels of airborne vanadium.[132] Toxic effects resulting from the intake of large amounts of vanadium in the diet are unlikely.[127,133] Vanadium deficiency in human is very rare and vanadium deficiency disease has not been identified in humans. The only epidemiological study in which an association between vanadium low intake and human cardiovascular disease is reported is that of Masironi.[134] Experimentally, vanadium compounds have been shown to be effective against many types of diseases including diabetes type 2, cancer, endemic tropical diseases, bacterial infections (tuberculosis and pneumonia), and HIV infections.[126,129] Furthermore, they can be operative in cardio- and neuroprotection. However, so far, vanadium compounds have not yet been approved as pharmaceuticals for clinical use.[126] The key facts on the probably essential trace elements are summarized in Table 2.

Potentially toxic elements

Fluorine

Fluorine (F) in the form of fluoride occurs in nature ubiquitously and enters the body through drinking waters and foods. Its concentration in water is very variable,[135] which explains much of the variability in total fluoride intake. Other important sources of fluoride are tea, seafood that contains edible bones or shells (e.g., canned sardines), and fluoridated tubes of toothpaste.[136] Most of ingested fluoride is absorbed from the upper intestines and is taken up by bones and teeth and the rest is lost in the urine.[137] Body fluoride status depends on multiple factors.[1,3,138] Fluorine has been suggested as a therapeutic agent in the treatment of osteoporosis. It is thought that fluoride in conjunction with calcium stimulates osteoblastic activity, increasing the hardness of bones. Low levels of fluorine in drinking water lead to dental decay[139,140] and possibly osteoporosis. High levels of dietary fluoride cause dental fluorosis and mottling of tooth enamel is a well-known feature of excess fluoride ingested.[1,140] Dental fluorosis may be easily recognized; however, the skeletal involvement is not clinically obvious until the advanced stage and early cases may be misdiagnosed as rheumatoid arthritis or osteoarthritis. 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.[141]

Lead

Lead or plumb (Pb) is the most important toxic heavy metal in the environment.[142] Important sources of environmental contamination include mining, smelting, manufacturing, and recycling activities. In addition, in some countries, the continued use of leaded paint, leaded gasoline, and leaded aviation fuel are other sources. More than three-quarters of global lead consumption are for the manufacture of lead-acid batteries for motor vehicles. Lead is also used in many other products, for example, pigments, paints, solder, stained glass, lead crystal glassware, ceramic glazes, jewelry, toys, and in some cosmetics and traditional medicines. Drinking water delivered through lead pipes or pipes joined with lead solder may also contain lead. An additional source of exposure is the use of certain types of unregulated cosmetics and medicines.[143] People can become exposed to inorganic lead through occupational inhalation (pulmonary absorption) of lead particles generated by burning materials containing lead and environmental sources from ingestion (gastrointestinal absorption) of lead-contaminated dust, water (from leaded pipes), and food (from lead-glazed or lead-soldered containers). Inorganic lead is not absorbed through the skin, although organic lead compounds are absorbed. The health effects of lead are the same regardless of the route of exposure.[144] Lead is a highly poisonous metal affecting almost every

Table 2: Key facts on probably essential elements

Element	Key facts	Bioavailability	Deficiency	Toxicity
Mn	Mn acts as activator of many enzymes and as a component of metalloenzymes like manganese superoxide dismutase, responsible for scavenging reactive oxygen species in mitochondrial oxidative stress. Homeostasis of iron and Mn is tightly interrelated.	Mn is absorbed through the GI tract and transported to organs enriched in mitochondria (in particular the liver, pancreas, and pituitary) where it is rapidly concentrated. Excretion of manganese is primarily through bile into the GI.	Mn deficiency in humans is very unusual. In experimental studies in humans, manganese deprivation was associated with scaly dermatitis and dyslipidemia.	Environmental or occupational Mn overexposure in at-risk populations is toxic. Excessive exposure to manganese may cause Parkinsonian-like motor and tremor symptoms and adverse cognitive effects.
Si	Si improves the structural integrity of skin, hair, nails, and bone calcification. Modulates the immune system and inflammatory response. Accelerates the rate of bone mineralization. Mitigates the risk of atherosclerosis. Si protects against the toxic actions of aluminum. The amount of silicon in tissues decreases with age.	Si compounds from food in the GI tract are hydrolyzed into bioavailable forms of silicic acid that diffuses into the blood circulation and it is distributed and accumulated into various tissues and organs. Si is filtered by the glomerulus because it does not form any bonds with plasma proteins. Silicon levels are higher in foods derived from plants.		
Ni	Ni has no clear biological function in the human body. However, it is in highest concentrations in the nucleic acids, particularly RNA, and is thought to be involved in protein structure and function. Ni may aid in prolactin production, and thus be involved in human breast milk production. Small quantities of Ni are essential for the body.	Humans may be exposed to Ni during breathing air, eating food, or smoking cigarettes. However, less than 10% of ingested Ni is absorbed by the GI tract.	Ni deficiency has not been shown to be a concern in humans.	Ni high uptakes can be toxic to human health. Occupational exposure to Ni and its compounds can cause allergic dermatitis known as "nickel allergy" in sensitized individuals.
B	B involves in steroid hormone metabolism, healthy bone development, and cell membrane maintenance. It is not accumulate in tissues. However, bone, nails, and hair have higher B levels, whereas fat tissue has low B levels.	B is ingested from the diet and absorbed from GI tract and presented in body as boric acid. It is excreted completely in the urine.	B deficiency is related to the decrease in the electrical activity of the brain, short-term memory, and decrease in skills in performing tasks. B deficiency is the possible causal agents in Kashin-Beck disease.	Environmental or industrial B exposure is not a treat for human health.
V	V is mainly found in bones, liver, and kidney.	Two main routes for the absorption of V are breathing and ingestion. V is also found in potable water and its intake by this source depends on the daily ingested volume.	V deficiency in human is very rare.	Toxic effects occur only as a result of industrial exposure to high levels of airborne V. Toxic effects resulting from the intake of large amounts of V in the diet are unlikely.

Mn=Manganese, Si=Silicon, Ni=Nickel, B=Boron, V=Vanadium, GI=Gastrointestinal tract

organ in the body. The nervous system is the most affected target in lead toxicity, both in children and adults. The toxicity in children is, however, of a greater impact than in adults, which may contribute to behavioral problems, learning deficits, and lowered IQ[142,145,146] because children absorb four to five times as much ingested lead as adults from a given source. In addition, children's innate curiosity and their age-appropriate hand-to-mouth behavior result in their mouthing and swallowing lead-containing or lead-coated objects. This route of exposure is magnified in children with a psychological disorder called Pica (persistent and compulsive cravings to eat nonfood items).[143] After absorption, 99% of the lead is bound to the hemoglobin portion of erythrocytes and is circulated

through the vascular system to soft tissues, liver, kidneys (organs of lead excretion), bone, and hair. During systemic circulation, lead interrupts the hemoglobin biosynthesis pathway primarily through inhibition of ∂-amino levulinic acid, an effect observed when blood lead level exceeds 5 μg/dL.[147] Elevated levels of zinc protoporphyrin (ZPP) often accompany elevated lead, and as such, ZPP is routinely included in testing for those who may be at risk for occupational exposure to lead. Interestingly, an elevated ZPP may increase the risk of lead exposure 6 months later.[148] The body stores lead in the teeth and bones, where it accumulates over time. Evidence supports that teeth and bone share similar qualities, such as a high affinity for metals and similar accumulation rates. The appearance of a "lead line" also known as a "Burtonian blue" line, at the gum line, is indicative of chronic lead poisoning.[149] The blue line is a common manifestation occurring in individuals with poor dental hygiene and is best described as the deposition of lead between collagen fibers', around blood vessels, and within cells.[150] Lead stored in bone may be remobilized into the blood during pregnancy, thus exposing the fetus.[151] Undernourished children are more susceptible to lead because their bodies absorb more lead if other nutrients, such as calcium or iron, are lacking. Children at highest risk are the very young (including the developing fetus) and the impoverished.[143] Lead exposure can have serious consequences for the health of children. At high levels of exposure, lead attacks the brain and central nervous system to cause coma, convulsions, and even death. Children who survive severe lead poisoning may be left with mental retardation and behavioral disorders. At lower levels of exposure that cause no obvious symptoms, lead is known to produce a spectrum of injury across multiple body systems. Lead also causes long-term harm in adults including anemia,[152] hypertension, renal impairment, immunotoxicity, and toxicity to the reproductive organs. The neurological and behavioral effects of lead are believed to be irreversible.[143] Exposure of pregnant women to high levels of lead can cause miscarriage, stillbirth, premature birth, and low birth weight. There is no known safe blood lead concentration. But it is known that as lead exposure increases, the range and severity of symptoms and effects also increase. Even blood lead concentrations as low as 5 μg/dL, once thought to be a "safe level," may be associated with decreased intelligence in children, behavioral difficulties, and learning problems.

Cadmium

Cadmium (Cd) is a trace element that is not believed to play a role in higher biologic systems or human nutrition. The primary source of cadmium exposure for nonsmokers is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes, grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium.[153] Tobacco leaves also accumulate high levels of cadmium from the soil, and thus regular use of tobacco-containing products is a common route of cadmium exposure for smokers. Smoking is estimated to at least double the lifetime body burden of cadmium exposure.[153] Following ingestion, it is estimated that 5%–10% of cadmium is absorbed.[154] In diets with low iron, calcium, or protein, it is possible that more cadmium is absorbed.[154] Ouch Ouch or Itai-Ita disease, which is unique to cadmium exposure due to long-term consumption of cadmium-contaminated rice, is characterized with renal tubular abnormalities and calcium and phosphate wasting resulting in severe osteomalacia and osteoporosis. But it has implications for aging patients in general who are diagnosed with osteoporosis as well.[155,156] In occupational work places such as battery, smelting, and electroplating industries, inhalation is the primary route of exposure where 5%–35% of inhaled cadmium is absorbed into the blood depending on its form, site of deposition, and particle size. If the cadmium penetrates to the alveoli, it is estimated that there is 100% absorption into the blood.[157] Dermal exposure is not a typical human health concern as cadmium does not penetrate the skin barrier.

Mercury

Mercury or hydrargyrium (Hg) is a common chemical exposure and environmental pollutant. It exists in organic and inorganic forms. The inorganic form could be further subdivided into elemental (or metallic/quicksilver) mercury and mercury salts. People may be exposed to mercury in any of its forms under different circumstances. However, exposure mainly occurs through consumption of fish and shellfish contaminated with methylmercury (organic mercury exposure) and through worker inhalation of elemental mercury vapors during industrial processing of amalgam and in the manufacture of scientific instruments and electrical control devices. Elemental and methylmercury are toxic to the central and peripheral nervous systems. Mercury vapor, in the atmosphere, is typically low and not considered a major route of exposure.[158] However, inhalation of mercury vapor can produce harmful effects on the nervous, digestive, immune systems, lungs, and kidneys, and may be fatal. The inorganic salts of mercury are corrosive to the skin, eyes, and gastrointestinal tract and may induce kidney toxicity if ingested. In addition, a study finding suggests that in experimental data from animal research and *in vitro* studies there are a strong influence of inorganic mercury on the nervous system. *In vitro* models showed all pathological changes seen in Alzheimer's disease (AD), and in animal models, inorganic mercury produced changes that are similar to those seen in AD. Its high affinity for selenium and selenoproteins suggests that inorganic mercury may promote neurodegenerative disorders through disruption of redox regulation. However, epidemiological and other studies suggest a much weaker relationship. It is likely that two processes play a modifying role here: humans may be differentially susceptible to mercury toxicity, when compared with other species, and some individuals might

be better able to chelate and detoxify mercury than others, reducing the strength of correlations between mercury exposure and AD.[159] Excretion of mercury depends on its original form. Elemental and inorganic salts are primarily excreted through the kidney and minimally through the gastrointestinal tract with a total half-life of 30–60 days. Excretion of organic mercury compounds is primarily fecal with enterohepatic recirculation leading to a longer half-life of approximately 70 days.[160,161]

Aluminium

Aluminium (Al) occurs naturally in the environment as hydroxides, oxides, and silicates. It also combines with other elements, such as sodium and fluoride, and as complexes with organic matter. Aluminium sulfate [$Al_2(SO_4)_3$] is a common additive to drinking water worldwide used as a "clarifying agent." Aluminium can enter the body through inhalation of dust and particles in the air, ingestion of food and water, dermal contact (cosmetic products), and drugs (antacid agents). Aluminium is poorly absorbed through ingestion and inhalation pathways and is essentially not absorbed dermally.[162-164] In the diet, aluminium bioavailability is highly dependent on its form and the presence of other food constituents with which it can form complexes, such as citric acid.[163] In an investigation, neurotoxic effects in dialysis patients treated with aluminium-containing dialysis fluids have been demonstrated[164] and it has been shown that following high aluminium dust exposures in the workplace can cause particle-related diseases called aluminosis. However, there is currently no evidence for an association between aluminium exposure and the development of breast cancer or AD.[164] The primary route of excretion for absorbed aluminium is through urine. Due to the natural presence of aluminium and its intake through common food items, all people will have some level of aluminium in their urine. In a survey of blood and urine levels of various metals, blood aluminium concentrations were typically less than 10 μg/dL.[165]

Arsenic

Arsenic (As) is widely distributed throughout the environment in the air, water, and soil. It is highly toxic in its inorganic form. Inorganic arsenic is a confirmed carcinogen and is the most significant chemical contaminant in drinking water globally. Arsenic can also occur in an organic form. Inorganic arsenic compounds (such as those found in water) are highly toxic, while organic arsenic compounds (such as those found in seafood) are less harmful to health. People are exposed to elevated levels of inorganic arsenic through drinking contaminated water, using contaminated water in food preparation and irrigation of food crops, industrial processes, eating contaminated food and smoking tobacco, breathing sawdust or burning smoke from arsenic-treated wood, living in an area with high levels of arsenic in rock, and working in a job where arsenic is made or used.[166] Exposure to arsenic can cause many health problems. Long-term exposure to inorganic arsenic, mainly through drinking-water and food, can lead to chronic arsenic poisoning, skin lesions, and skin cancer.[166] The first symptoms of long-term exposure to high levels of inorganic arsenic are usually observed in the skin and include pigmentation changes, skin lesions, and hard patches on the palms and soles of the feet (hyperkeratosis). These occur after a minimum exposure of approximately 5 years and may be a precursor to skin cancer. Being exposed to low levels for a long time can change the color of the skin. It can cause corns and small warts. In addition to skin cancer, long-term exposure to arsenic may also cause cancers of the bladder and lungs. The International Agency for Research on Cancer (IARC) has classified arsenic and arsenic compounds as carcinogenic to humans and has also stated that arsenic in drinking water is carcinogenic to humans. Arsenic is also associated with adverse pregnancy outcomes and infant mortality, with impacts on child health,[167] and exposure *in utero* and early childhood has been linked to increases in mortality in young adults due to multiple cancers, lung disease, heart attacks, and kidney failure.[168] Numerous studies have demonstrated negative impacts of arsenic exposure on cognitive development, intelligence, and memory.[169] Almost no information is available on the effects of organic arsenic compounds in humans. Studies in animals show that most simple organic arsenic compounds (such as methyl and dimethyl compounds) are less toxic than the inorganic forms.[170] Both inorganic and organic forms leave the body through urine. Most of the inorganic arsenic will be gone within several days, although some will remain in the body for several months or even longer. If one is exposed to organic arsenic, most of it will leave the body within several days.[170] Despite the toxicity of arsenic, arsenic trioxide has been used in a number of traditional Chinese medicines to treat cancer.[171] Previous studies have identified that arsenic trioxide induces apoptosis in acute promyelocytic leukemia cells,[172,173] glioblastoma cells,[174] and gastric cancer cells[175] and inhibits cell growth in breast cancer.[176] The use of arsenic trioxide is also being evaluated for the treatment of certain malignancies, including lung cancer[177] and hepatocellular cancer.[178] Although arsenic trioxide exhibits a significant antitumor function in multiple cancer types, it is concluded that its exact effect on lymphoma and the underlying mechanism of action remain under investigation.[179]

Tin

Tin or stannum (Sn) is used principally in food industry to line canned food and beverages and this represents the major route of human exposure to it. In addition, tin has been proposed for use as a corrosion inhibitor.[180] There is no evidence that tin is an essential element for humans. Tin as single atoms or molecules is not very toxic to any kind of organism. The toxic form is the organic form (organotin), and

Table 3: Key facts on potentially toxic elements

Element	Key facts	Bioavailability	Deficiency	Toxicity
F	F in the form of fluoride occurs in nature ubiquitously. F has been suggested as a therapeutic agent in the treatment of osteoporosis.	F enters the body through drinking waters and foods. Other important sources of F are tea, seafood, and toothpastes. Most of the ingested F is absorbed from the upper intestines and is taken up by bones and teeth and the rest is lost in the urine.	Low levels of F in drinking water lead to dental decay.	High levels of dietary F cause dental fluorosis and mottling of tooth enamel is a well-known feature of excess F ingested.
Pb	Pb is a toxic element that affects multiple body systems and is particularly is harmful to young children. Human exposure is usually assessed through the measurement of Pb in whole blood. There is no known level of Pb exposure that is considered safe.	After absorption, 99% of Pb is bound to the hemoglobin portion of erythrocytes and is circulated via the vascular system to soft tissues, liver kidneys, bone, brain, and hair. Pb is stored in the teeth and bones, where it accumulates over time. Pb in bone is released into blood during pregnancy that becomes a source of exposure to the developing fetus.		Appearance of a "lead line" also known as a "Burtonian blue" line, at the gum line, is indicative of chronic lead poisoning. Long-term exposure in adults causes anemia, hypertension, renal impairment, immunotoxicity, and toxicity to the reproductive organs. The neurological and behavioral effects of lead are irreversible.
Cd	Cd does not play a role in higher biologic systems or human nutrition. Dermal exposure is not a typical human health concern as Cd does not penetrate the skin barrier.	The primary source of Cd exposure for nonsmokers is from the food supply in general, leafy vegetables. Regular use of tobacco-containing products is a common route of cadmium exposure for smokers.		In occupational work places inhalation is the primary route of exposure. Ouch Ouch or Itai-Ita disease is unique to long-term consumption of Cd-contaminated rice.
Hg	Hg is a common chemical exposure and environmental pollutant. It exists in organic and inorganic forms. Elemental and methylmercury are toxic to the central and peripheral nervous systems.	Exposure mainly occurs through consumption of contaminated fish and shellfish and through worker inhalation. Excretion of Hg depends on its original form.		Mercury vapor, in the atmosphere, is typically low and not considered a major route of exposure.
Al	Aluminum sulfate is a common additive to drinking water worldwide used as a "clarifying agent." Due to Al intake through common food items, all people have some level of Al in their urine.	Al is poorly absorbed via ingestion and inhalation and is essentially not absorbed dermally. Excretion for absorbed Al is through urine.		Neurotoxic effects of Al in dialysis patients treated with Al-containing dialysis fluids have been demonstrated.
As	As is highly toxic and exists in inorganic and organic forms. Inorganic As is the most significant chemical contaminant in drinking-water globally.	Both inorganic and organic As forms leave the body through urine.		Inorganic As is toxic and is a confirmed carcinogen. Organic As compounds are less harmful. Long-term exposure to inorganic As, mainly through drinking water and food, can lead to chronic arsenic poisoning, skin lesions, and skin cancer.

Contd...

Table 3: Contd...

Element	Key facts	Bioavailability	Deficiency	Toxicity
Sn	Sn is used in food industry to line canned food and beverages and this is the major route of human exposure to it. Sn as single atoms or molecules is not very toxic to any kind of organism.	Sn and inorganic Sn compounds are poorly absorbed from the GI tract after oral (eating/drinking) or inhalation (breathing in) and dermal exposure (skin contact) and they do not accumulate in tissues. They are rapidly excreted, primarily in the feces, and therefore, they do not usually cause harmful effects.	There is no evidence that Sn is an essential element for humans.	Toxic form of Sn is the organic form (organotin) and its toxicity has been epidemiologically linked to several markers of impaired health and growth in animal models.
Li	Li is the first choice in treating bipolar disorders. Li has beneficial pharmacological properties (antimanic).	Lithium absorption is through the GI.		Individuals may stop their treatment at some point. Three organ systems that may be negatively affected by Li in long-term use are the thyroid gland, kidneys, and parathyroid gland.

F=Fluorine, Pb=Lead, Cd=Cadmium, Hg=Mercury/hydrargyrium, Al=Aluminium, As=Arsenic, Sn=Stannum/tin, Li=Lithium, GI=Gastrointestinal tract

its toxicity, on the other hand, has been epidemiologically linked to several markers of impaired health and growth in animal models.[181] Tin and inorganic tin compounds are poorly absorbed from the gastrointestinal tract after oral (eating/drinking) or inhalation (breathing in) and dermal exposure (skin contact) and they do not accumulate in tissues. They are rapidly excreted, primarily in the feces, and therefore, they do not usually cause harmful effects. The main adverse effect on humans of excessive levels of tin in canned beverages (above 150 mg/kg) or other canned foods (above 250 mg/kg) has been acute gastric irritation. There is no evidence of adverse effects in humans associated with chronic exposure to tin. In addition, for the general population, drinking water is not a significant source of tin.[181,182] There is no evidence that inorganic tin compounds affect reproductive functions, produce birth defects, or cause genetic changes. Inorganic tin compounds are not known to cause cancer.[181-183]

Lithium

Lithium (Li) gets its name from "lithos," the Greek word for stone, because it is present in trace amounts in virtually all rocks.[184] Lithium remains the first choice in treating bipolar disorders. Yet, about half of all individuals may stop their treatment at some point. Although this observation is multi-factorial, one obvious potential contributor is the side effect and toxicity burden associated with lithium.[185-187] The three organ systems that may be negatively affected by lithium in long-term use are the thyroid gland, kidneys, and parathyroid gland.[185] The prevalence of lithium-induced thyroid hypothyroidism, as an example, in lithium-treated patients varies substantially across studies reflecting both different populations and varying definitions of hypothyroidism.[76,185,188] The most important risk factors for lithium-induced hypothyroidism are the presence of antithyroid antibodies, which increases the risk by eightfold.[76,185,189,190] Lithium absorption is through the gastrointestinal tract and blood levels peak after single oral doses of lithium are between 2 and 4 h. Accordingly, in clinical practice, blood lithium levels are measured at least 8 h after the last dose to avoid sampling during these peaks.[191] The key facts on probably toxic elements are summarized in Table 3.

Results and Conclusion

Trace elements (or trace minerals) are usually defined as minerals that are required in amounts between 1 and 100 mg/day by adults or make up less than 0.01% of total body weight.[1-3] Ultra-trace minerals generally are defined as minerals that are required in amounts less than 0/001 mg/day. This review is an update of the previously published article in 2013. The previous review was updated to emphasis in detail the importance of known trace elements so far in humans' physiology and nutrition, and also to implement the detailed information for practical and effective management of trace elements' status in clinical diagnosis and healthcare situations. In addition, it applied WHO classification for trace elements' classification as previously done.[3] In this classification, the trace elements have been divided into three groups from the point of their nutritional significance in humans, as follows: (1) essential elements; (2) elements which are probably essential; and (3) potentially toxic elements, some of which may nevertheless have some essential functions at even low levels. Homoeostasis for different trace elements is maintained by different mechanisms regulating absorption or excretion in response to changes in nutritional status.

For the past decades, the biological role, biochemical functions, signs of excess, and deficiency of the essential trace or ultra-trace elements in humans are studied and identified in depth. For these elements, essentiality and

toxicity are unrelated and toxicity is a matter of dose or exposure. Little is known about the essentiality of some of the probably essential elements such as vanadium, boron, and nickel in advanced organisms and humans' physiology and possibly treatment of diseases. For toxic heavy metals, a toxic element may nevertheless be essential; however, two elements with beneficial pharmacological properties are lithium (antimanic) and fluorine (anticariogenic). Investigations indicated that for most of the trace-element-related disorders,[2,3] the pathological manifestations will remain difficult to detect until more specific pathologically relevant indicators of deficiency or excess become available. In addition, researchers indicated the chemical and physiological factors may modify the bioavailability of trace elements in the diet and influence the risk of trace-element-related diseases.[3] Discoveries and many refinements in the development of new techniques and continual improvement in laboratory methods have enabled researchers to detect the early pathological consequences of deficiency or excess of trace elements. They all are promises to fulfill the gaps in the present and future research and clinical diagnosis of trace elements deficiencies or intoxications. However, further investigations are needed to complete important gaps in our knowledge on trace elements especially probably essential trace elements role in health and disease status.

Financial support and sponsorship

Nil.

Conflict of interest

There is no conflict of interest.

Received: 06 Feb 19 **Accepted:** 14 Oct 19
Published: 03 Jan 20

References

1. Aliasgharpour M, Farzami MR. Trace elements in human nutrition: A review. Int J Med Invest 2013;2:115-28.
2. Frieden E. New perspective on the essential trace elements. J Chem Educ 1985;62:917-23.
3. Trace elements in human nutrition and health. Geneva: World Health Organization; 1996.
4. Ali A, Ma Y, Reynolds J, Wise JP Sr, Inzucchi SE, Katz DL. Chromium effects on glucose tolerance and insulin sensitivity in persons at risk for diabetes mellitus. Endocr Pract 2011;17:16-25.
5. Mikulewicz M, Chojnacka K, Kawala B, Gredes T. Trace elements in living systems: From beneficial to toxic effects. Hindawi Bio Med Res Inter 2017;2017:8297814. doi: 10.1155/2017/8297814.
6. Staniek H, Wójciak RW. The combined effects of iron excess in the diet and chromium (III) supplementation on the iron and chromium status in female rats. Biol Trace Elem Res 2018;184:398-408.
7. Bjørklund G, Aaseth J, Skalny AV, Suliburska J, Skalnaya MG, Nikonorov AA, *et al*. Interactions of iron with manganese, zinc, chromium, and selenium as related to prophylaxis and treatment of iron deficiency. J Trace Elem Med Biol 2017;41:41-53.
8. Offenbacher EG. Chromium in the elderly. Biol Trace Elem Res 1992;32:123-31.
9. Food and Nutrition Board of the Institute of Medicine. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academies Press; 2000.
10. Brown RO, Brown RO, Forloines-Lynn S, Cross RE, Heizer WD. Chromium deficiency after long term total parenteral nutrition. Dig Dis Sci 1986;31:661-4.
11. Jeejeebhoy KN, Chu RC, Marliss EB, Greenberg GR, Bruce-Robertson A. Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parenteral nutrition. Am J Clin Nutr 1977;30:531-8.
12. Gad SC. Acute and chronic systemic chromium toxicity. Sci Total Environ 1989;86:149-57.
13. United States Environmental Protection Agency. Toxicological review of hexavalent chromium. CAS No.(8540-29-9). Washington, DC: US Environmental Protection Agency; 1998.
14. Mackenzie RD, Byerrum RU, Decker CF, Hoppert CA, Langham RF. Chronic toxicity studies. II. Hexavalent and trivalent chromium administrated in drinking water to rats. AMA Arch of Indust Health 1958;18:232-4.
15. Prohaska JR. Biochemical functions of copper in animals. In: Prasad AS, editor Essential and Toxic Trace Elements in Human Health and Disease. New York, NY: Alen R Liss; 1988.
16. Danks DM. Copper deficiency in humans. Annu Rev Nutr 1988;8:235.
17. Turnlund JR. Copper nutriture, bioavailability and the influence of dietary factors. J Am Diet Assoc 1988;88:303-8.
18. Turnlund JR, King JC, Gong B, Keyes WR, Michel MC. A stable isotope study of copper absorption 111 young men: Effect of phytate and X-cellulose. Am J Clin Nutr 1985;42:18-23.
19. Sandstead HH. Copper bioavailability and requirements. Am J Clin Nutr 1982;32:908-14.
20. Chan WY, Rennert OM. The role of copper in iron metabolism. Ann Clin Lab Sci 1980;10:338-44.
21. Harris ED. The iron-copper connection: The link to ceruloplasmin grows stronger. Nutr Rev 1995;53:170-3.
22. Johnson MA, Kays SE. Copper: Its role in human nutrition. Nutr Today 1990;25:6.
23. Mercer JF. The molecular basis of copper-transport diseases. Trends Mol Med 2001;7:64-9.
24. Verrotti A, Carelli A, Coppola G. Epilepsy in children with Menkes disease: A systematic review of literature. J Child Neurol 2014;29:1757-64.
25. Milne BD. Trace elements. In: Burtis CA, Ashwood ER, editors. Tietz Textbook of Clinical Chemistry. 2nd ed. USA: Saunders Co.; 1994. p. 1335-38.
26. Loudianos G, Lepori MB, Mameli E, Dessì V, Zappu A. Wilson's disease. Prilozi 2014;35:93-8.
27. Nastoulis E, Karakasi MV, Couvaris CM, Kapetanakis S, Fiska A, Pavlidis P. Greenish-blue gastric content: Literature review and case report on acute copper sulphate poisoning. Forensic Sci Rev 2017;29:77-9.
28. Aliasgharpour M. A review on copper, ceruloplasmin and Wilson's disease. Int J Med Invest 2015;4:344-7.
29. Satyanarayana U, Chakrapani U. Essentials of biochemistry. 2nd ed. Kolkata: Arunabha Sen Book and Allied (P) Ltd.; 2008. p. 210-27.
30. Zalewski PD, Forbes IJ, Giannakis C. Physiological role for zinc in prevention of apoptosis (gene-directed death). Biochem Int 1991;241093-101.

31. Klug A, Schwabe JW. Protein motifs 5. Zinc fingers. FASEB J 1995;9:597-604.
32. Franklin RB, Costello LC. Zinc as an anti-tumor agent in prostate cancer and in other cancers. Arch Biochem Biophys 2007;463:211-7.
33. Das M, Das R. Need of education and awareness towards zinc supplementation: A review. Int J Nutr Metab 2012;4:45-50.
34. Iannotti LL, Zavaleta N, León Z, Huasquiche C, Shankar AH, Caulfield LE. Maternal zinc supplementation reduces diarrheal morbidity in peruvian infants. J Pediatr 2010;156:960-4.e2.
35. Aliasgharpour M. Zn Status in gastroenteritis children under five years old. Int J Med Invest 2015;4:180-2.
36. Lee HH, Prasad AS, Brewer GJ, Owyang C. Zinc absorption in human small intestine. Am J Physiol 1989;256:G87-91.
37. Lönnerdal B. Dietary factors influencing zinc absorption. J Nutr 2000;130:1378S-83S.
38. Tuormaa TE. Adverse effects of zinc deficiency: A review from the literature. J Orthomol Med 1995;10:149-64.
39. Küry S, Dréno B, Bézieau S, Giraudet S, Kharfi M, Kamoun R, *et al*. Identification of SLC39A4, a gene involved in acrodermatitis enteropathica. Nat Genet 2002;31:239-40.
40. Wastney ME, Ahmed S, Henkin RI. Changes in regulation of human zinc metabolism with age. Am J Physiol 1992;263:R1162-8.
41. King JC, Klein CL. Zinc. In: Shils ME, Olson JA, Shike M, editors. Modern Nutrition in Health and Disease. Philadelphia: Lippincott; 2000. p. 223.
42. Turnlund JR, Durkin N, Costa F, Margen S. Stable isotope studies of zinc absorption and retention in young and elderly men. J Nutr 1986;116:1239-47.
43. Patterson WP, Winkelmann M, Perry MC. Zinc-induced copper deficiency: Mega mineral sideroblastic anemia. Ann Intern Med 1985;103:385-6.
44. Yadrick MK, Kenney MA, Winterfeldt EA. Iron, copper, and zinc status: Response to supplementation with zinc or zinc and iron in adult females. Am J Clin Nutr 1989;49:145-50.
45. Walter RM Jr, Uriu-Hare JY, Olin KL, Oster MH, Anawalt BD, Critchfield JW, *et al*. Copper, zinc, manganese, and magnesium status and complications of diabetes mellitus. Diabetes Care 1991;14:1050-6.
46. Cunningham JJ, Fu A, Mearkle PL, Brown RG. Hyperzincuria in individuals with insulin-dependent diabetes mellitus: Concurrent zinc status and the effect of high-dose zinc supplementation. Metabolism 1994;43:1558-62.
47. Rotruck JT, Pope AL, Ganther HE, Swanson AB, Hafeman DG, Hoekstra WG. Selenium: Biochemical role as a component of glutathione peroxidase. Science 1973;179:588-90.
48. Hatfield DL, Tsuji PA, Carlson BA, Gladyshev VN. Selenium and selenocysteine: Roles in cancer, health, and development. Trends Biochem Sci 2014;39:112-20.
49. Gladyshev VN, Martin-Romero FJ, Xu XM, Kumaraswamy E, Carlson BA, Hatfield DL, *et al*. Molecular biology of selenium and its role in cancer, AIDS and other human diseases. Recent Res Develop Biochem 1999;1:145-67.
50. Skalny AV. Bioelements and bioelementology in pharmacology and nutrition: Fundamental and practical aspects. In: Atroshi F, editor. Pharmacology and Nutritional Intervention in the Treatment of Disease. In Tech Publisher; 2014.
51. Skalnaya MG, Skalny AV. Essential Trace Elements in Human Health: A Physician's View. Tomsk Publishing House of Tomsk State University; 2018.
52. Misra S, Kwong RW, Niyogi S. Transport of selenium across the plasma membrane of primary hepatocytes and enterocytes of rainbow trout. J Exp Biol 2012;215:1491-501.
53. Combs GF Jr. Biomarkers of selenium status. Nutrients 2015;7:2209-36.
54. Yang W, Diamond AM. Selenium-binding protein 1 as a tumor suppressor and a prognostic indicator of clinical outcome. Biomark Res 2013;1:15.
55. Verma S, Hoffmann FW, Kumar M, Huang Z, Roe K, Nguyen-Wu E, *et al*. Selenoprotein K knockout mice exhibit deficient calcium flux in immune cells and impaired immune responses. J Immunol 2011;186:2127-37.
56. Bellinger FP, Raman AV, Reeves MA, Berry MJ. Regulation and function of selenoproteins in human disease. Biochem J 2009;422:11-22.
57. Huang Z, Rose AH, Hoffmann PR. The role of selenium in inflammation and immunity: From molecular mechanisms to therapeutic opportunities. Antioxid Redox Signal 2012;16:705-43.
58. Schoenmakers E, Agostini M, Mitchell C, Schoenmakers N, Papp L, Rajanayagam O, *et al*. Mutations in the selenocysteine insertion sequence-binding protein 2 gene lead to a multisystem selenoprotein deficiency disorder in humans. J Clin Invest 2010;120:4220-35.
59. Levander OA. Selenium: Biochemical actions, interactions and some human health implications. In: Prasad AS, editor. Clinical, Biochemical and Nutritional Aspects of Trace Elements. New York: Alan R Liss; 1982. p. 345-68.
60. Muth OH, Oldfield JE, Remmert LF, Schubert JR. Effects of selenium and vitamin E on the muscle disease. Science 1958;128:1090.
61. Novotny JA, Peterson CA. Molybdenum. Adv Nutr 2018;9:272-3.
62. Chan S, Gerson B, Subramaniam S. The role of copper, molybdenum, selenium, and zinc in nutrition and health. Clin Lab Med 1998;18:673-85.
63. Turnlund JR, Keyes WR, Peiffer GL. Molybdenum absorption, excretion, and retention studied with stable isotopes in young men at five intakes of dietary molybdenum. Am J Clin Nutr 1995;62:790-6.
64. Anke MK. Molybdenum. In: Merian E, Anke M, Ihnat M, Stoeppler M, editors. Elements and Their Compounds in the Environment. Weinheim: Wiley-VCH Verlag; 2004. p. 1007-37.
65. Ichida K, Amaya Y, Okamoto K, Nishino T. Mutations associated with functional disorder of xanthine oxidoreductase and hereditary xanthinuria in humans. Int J Mol Sci 2012;13:15475-95.
66. Agarwal A, Banerjee A, Banerjee UC. Xanthine oxidoreductase: A journey from purine metabolism to cardiovascular excitation-contraction coupling. Crit Rev Biotechnol 2011;31:264-80.
67. Lewander WJ, Lacouture PG, Silva JE, Lovejoy FH. Acute thyroxine ingestion in pediatric patients. Pediatrics 1989;84:262-5.
68. Fisher DA. Delange F. Thyroid hormone and iodine requirements in man during brain development. In: Stanbury JB, John B (John Burton). editors. Iodine in Pregnancy. Delhi: Oxford University Press; 1998. p. 1-33.
69. Delange F, Bourdoux P, Chanoine JP, Ermans AM. Physiopathology of iodine nutrition during pregnancy, lactation and early postnatal life. In: Berger H, editor. Vitamins and Minerals in Pregnancy and Lactation. New York, NY: Raven Press; 1988. p. 205-14.
70. Kucharzewski M, Braziewicz J, Majewska U, Góźdź S. Concentration of selenium in the whole blood and the thyroid tissue of patients with various thyroid diseases. Biol Trace Elem Res 2002;88:25-30.
71. Prete A, Paragliola RM, Corsello SM. Iodine supplementation:

Usage "with a grain of salt." Int J Endocrinol 2015;2015:312305.
72. Pearce EN. Iodine deficiency in children. Endocr Dev 2014;26:130-8.
73. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 2015;3:286-95.
74. Führer D, Mann K, Feldkamp J, Krude H, Spitzweg C, Kratzsch J, *et al*. Thyroid dysfunction in pregnancy. Dtsch Med Wochenschr 2014;139:2148-52.
75. Li JH, He ZH, Bansal V, Hennessey JV. Low iodine diet in differentiated thyroid cancer: A review. Clin Endocrinol (Oxf) 2016;84:3-12.
76. Aliasgharpour M, Abbassi M, Shafaroodi H, Razi F. Subclinical hypothyroidism in lithium treated psychiatric patients in Tehran, Islamic Republic of Iran. Eastern Mediterranean Health J 2005;11:329-33.
77. Kopp P. Thyrotoxicosis of other etiologies. In: De Groot LJ, Beck-Peccoz P, Chrousos G, Dungan K, Grossman A, Hershman JM, *et al*. editors. Endotext (Comprehensive Free Online Endocrinology Book). South Dartmouth, MA: MDText.com. Inc.; 2000. Available from: http://www.ncbi.nlm.nih.gov/books/NBK285562. [Last accessed on 2019 Jan 15].
78. Xu S, Chen G, Peng W, Renko K, Derwahl M. Oestrogen action on thyroid progenitor cells: Relevant for the pathogenesis of thyroid nodules? J Endocrinol 2013;218:125-33.
79. Aschner JL, Aschner M. Nutritional aspects of manganese homeostasis. Mol Aspects Med 2005;26:353-62.
80. Li L, Yang X. The essential element manganese, oxidative stress, and metabolic diseases: Links and interactions. Oxid Med Cell Longev 2018;2018:7580707. doi: 10.1155/2018/7580707.
81. Friedman BJ, Freeland-Graves JH, Bales CW, Behmardi F, Shorey-Kutschke RL, Willis RA, *et al*. Manganese balance and clinical observations in young men fed a manganese-deficient diet. J Nutr 1987;117:133-43.
82. Bailey LA, Kerper LE, Goodman JE. Derivation of an occupational exposure level for manganese in welding fumes. Neurotoxicology 2018;64:166-76.
83. Kornblith ES, Casey SL, Lobdell DT, Colledge MA, Bowler RM. Environmental exposure to manganese in air: Tremor, motor and cognitive symptom profiles. Neurotoxicology 2018;64:152-8.
84. Madejczyk MS, Ballatori N. The iron transporter ferroportin can also function as a manganese exporter. Biochim Biophys Acta 2012;1818:651-7.
85. Yin Z, Jiang H, Lee ES, Ni M, Erikson KM, Milatovic D, *et al*. Ferroportin is a manganese-responsive protein that decreases manganese cytotoxicity and accumulation. J Neurochem 2010;112:1190-8.
86. Jugdaohsingh R, Anderson SH, Tucker KL, Elliott H, Kiel DP, Thompson RP, *et al*. Dietary silicon intake and absorption. Am J Clin Nutr 2002;75:887-93.
87. Popplewell JF, King SJ, Day JP, Ackrill P, Fifield LK, Cresswell RG, *et al*. Kinetics of uptake and elimination of silicic acid by a human subject: A novel application of 32Si and accelerator mass spectrometry. J Inorg. Biochem 1998;69:177-80.
88. Jugdaohsingh R. Silicon and bone health. J Nutr Health Aging 2007;11:99-110.
89. Martin KR. The chemistry of silica and its potential health benefits. J Nutr Health Aging 2007;11:94-7.
90. Martin KR. Dietary silicon: Is biofortification essential? J Nutr and Food Sci Forecast 2018;1:1006.
91. Nakanishi L, Bombonatti B, Muller LS, Villa RT, Velasco MV, Bedin V, *et al*. Oral supplementation of orthosilicic acid and its impact on hair quality. Med Cutan Iber Lat Am 2017;45:29-35.
92. Sripanyakorn S, Jugdaohsingh R, Thompson RPH, Powell JJ. Dietary silicon and bone health. Nutr Bull 2005;30:222-30.
93. Perry CC. Keeling-Tucker. Aspects of the bioinorganic chemistry of silicon in conjunction with the biometals calcium, iron and aluminum. J Inorg Biochem 1998;69:181-91.
94. Reffitt DM, Jugdaohsingh R, Thompson RP, Powell JJ. Silicic acid: Its gastrointestinal uptake and urinary excretion in man and effects on aluminum excretion. J Inorg Biochem 1999;76:141-7.
95. D'Imperio M, Brunetti G, Gigante I, Serio F, Santamaria P, Cardinali A, *et al*. Integrated *in vitro* approaches to assess the bioaccessibility and bioavailability of silicon-biofortified leafy vegetables and preliminary effects on bone. *In Vitro* Cell Dev Biol Anim 2017;53:217-24.
96. Chen F, Cole P, Wen L, Mi Z, Trapido EJ. Estimates of trace element intakes Chinese farmers. J Nutr 1994;124:196-201.
97. Anderson JJ. Plant-based diets and bone health: Nutritional implications. Am J Clin Nutr 1999;70:539S-42S.
98. Anke M, Angelow L, Glei M, Müller M, Illing H. The biological importance of nickel in the food chain. Fresenius J Anal Chem 1995;352:92-6.
99. Anke MB, Groppel B, Kronemann H, Grün M. Nickel – An essential element. IARC; 1984. p. 339-65.
100. Poonkothai M, Vijayavathi S. Nickel as an essential element and a toxicant. Inter J Engin Sci and Tech 2012;1:285-8.
101. Sydor AM, Zamble DB. Nickel metallomics: General themes guiding nickel homeostasis. In: Banci L, editor. Metallomics and the Cell. Met Ions Life Sci. Dordrecht: Springer; 2013. p. 375-416.
102. International Program on Chemical Safety (IPCS). Environmental Health Criteria 108: Nickel, Geneva: World Health Organization; 1992.
103. Barceloux DG. Nickel. Clin Toxicol 1999;37:239-58.
104. Thyssen JP, Linneberg A, Menné T, Johansen JD. The epidemiology of contact allergy in the general population-prevalence and main findings. Contact Dermatitis 2007;57:287-99.
105. Hostynek JJ, Maibach HL. Nickel and the Skin. Boca Raton, FL: CRC Press; 2002. p. 1-249.
106. Goldbach HE, Wimmer MA. Boron in plants and animals: Is there a role beyond cell-wall structure? J. Plant Nutr. Soil Sci.-Zeitschrift Fur Pflanzenernahrung Und Bodenkunde 2007;170:39-48.
107. Hunt CD. Regulation of enzymatic activity – One possible role of dietary boron in higher animals and humans. Biol Trace Elem Res 1998;66:205-25.
108. Hunt CD. Biochemical effects of physiological amounts of dietary boron. J Trace Elem Exp Med 1996;9:185-213.
109. Cui Y, Winton MI, Zhang ZF, Rainey C, Marshall J, De Kernion JB, *et al*. Dietary boron intake and prostate cancer risk. Oncol Rep 2004;11:887-92.
110. Tanaka M, Fujiwara T. Physiological roles and transport mechanisms of boron: Perspectives from plants. P flugers Arch Eur J Physiol 2008;456:671-7.
111. Ku WW, Chapin RE, Moseman RF, Brink RE, Pierce KD, Adams KY. Tissue disposition of boron in male Fischer rats. Toxicol Appl Pharmacol 1991;111:145-1.
112. Baker SJ, Tomsho JW, Benkovic SJ. Boron-containing inhibitors of synthetases. Chem Soc Rev 2011;40:4279-85.
113. Pahl MV, Culver BD, Strong PL, Murray FG, Vaziri ND. The effect of pregnancy on renal clearance of boron in humans: A study based on normal dietary intake of boron. Toxicol Sci 2001;60:252-6.
114. Kot FS. Boron sources, speciation and its potential impact of health. Rev Environ Sci Bio/Technol 2009;8:3-28.

115. Sayli BS. An assessment of fertility in boron-exposed Turkish subpopulations – 2. Evidence that boron has no effect on human reproduction. Biol Trace Elem Res 1998;66:409-22.
116. Sayli BS, Tuccar E, Elhan AH. An assessment of fertility in boron-exposed Turkish subpopulations. Reprod Toxicol 1998;12:297-304.
117. Duydu Y, Başaran N, Bolt HM. Exposure assessment of boron in Bandırma boric acid production plant. J Trace Elem Med Biol 2012;26:161-4.
118. Litovitz TL, Klein-Schwartz W, Oderda GM, Schmitz BF. Clinical manifestations of toxicity in a series of 784 boric acid ingestions. Am J Emerg Med 1988;6:209-13.
119. Nielsen FH. Boron in human and animal nutrition. Plant Soil 1997;193:199-208.
120. Murray FJ. A human health risk assessment of boron (boric acid and borax) in drinking water. Regul Toxicol Pharm 1995;22:221-30.
121. Penland JG. Dietary boron, brain-function, and cognitive performance. Environ Health Perspect 1994;102:65-72.
122. Penland JG. The importance of boron nutrition for brain and psychological function. Biol Trace Elem Res 1998;66:299-317.
123. Peng X, Zeng LX, Schrauzer GN, Xiong G. Selenium, boron, and germanium deficiency in the etiology of Kashin-Beck disease. Biol Trace Elem Res 2000;77:193-7.
124. Rehder D. Inorganic and coordination compounds of vanadium. In: Woollins D, Crabtree B, Atwood D, Meyer G, editors. Bioinorganic vanadium chemistry. New York: Wiley and Sons, Ltd.; 2008. p. 13-49.
125. Rehder D. The role of vanadium in biology. Metallomics 2015;7:730-42.
126. Rehder D. Perspectives for vanadium in health issues. Future Med Chem 2016;8:325-38.
127. Agency for Toxic Substance and Disease Registry (ATSDR). U.S. Toxicological Profile for Vanadium. Atlanta, GA: Department of Health and Humans Services, Public Health Service, Centers for Disease Control; 2012.
128. Levina A, McLeod AI, Kremer LE, Aitken JB, Glover CJ, Johannessen B, *et al*. Reactivity-activity relationships of oral anti-diabetic vanadium complexes in gastrointestinal media: An X-ray absorption spectroscopic study. Metallomics 2014;6:1880-8.
129. Rehder D. The potentiality of vanadium in medicinal applications. Future Med Chem 2012;4:1823-37.
130. Costa-Pessoa J, Tomaz I. Transport of therapeutic vanadium and ruthenium complexes by blood plasma components. Curr Med Chem 2010;17:3701-38.
131. Kordowiak AM, Baranowska-Bosiacka I, Gutowska I, Chlubek D. Biochemical and medical importance of vanadium compounds. Acta Biochim Pol 2012;59:195-200.
132. Li H, Zhou D, Zhang Q, Feng C, Zheng W, He K, *et al*. Vanadium exposure-induced neurobehavioral alterations among Chinese workers. Neurotoxicology 2013;36:49-54.
133. Ma J, Pan LB, Wang Q, Lin CY, Duan XL, Hou H. Estimation of the daily soil/dust (SD) ingestion rate of children from Gansu Province, China via hand-to-mouth contact using tracer elements. Environ Geochem Health 2018;40:295-301.
134. Masironi R. Trace elements and cardiovascular diseases. Bull World Health Organ 1969;40:305-12.
135. Stamp TC. Fluoride. In: Macrae R, Robinson RK, Sadler MJ, editors. Encyclopedia of Food Science, Food Technology, and Nutrition. London: Academic Press; 1993. p. 1932.
136. Recommended Dietary Allowances. Editors; National Research Council (US) Subcommittee on the 10th ed. of the Recommended Dietary Allowances. Washington, DC: National Academies Press (US); 1989.
137. National academies of sciences engineering and medicine: Fluoride in Drinking Water. A Scientific Review of EPA's Standards; 2006.
138. Nguta JM. Essential Trace Elements: Trace Elements in Human and Animal Health. Germany: LAP, Lambert Academic Publishing; 2010.
139. Mellberg JR, Ripa LW. Flouride Metabolism. Fluorides in Preventive Dentistry-Theory and Clinical Applications. Chicago: Quintessence publishing Co. Limited; 1983. p. 81-102.
140. Kaminsky LS, Mahoney MC, Leach J, Melius J, Miller MJ. Fluoride: Benefits and risk of exposure. Crit Rev Oral Biol Med 1990;1:261-81.
141. Prashanth L, Kattapagari KK, Chitturi RT, Baddam VR, Prasad LK. A review on the role of essential trace elements in health and disease. JNTR Univ Health Sci 2015;4:75-85.
142. Patrick L. Lead toxicity, a review of the literature. Part 1: Exposure, evaluation, and treatment. Altern Med Rev 2006;11:2-22.
143. Lead poisoning and health. Media center/WHO fact sheet. Available from: http://www.who.int/mediacentre/factsheets/fs379/en/.2017. [Last accessed on 2019 Jan 10].
144. Agency for Toxic Substance and Disease Registry (ATSDR), U.S. Toxicological Profile for Lead; 2007. Available from: https://www.atsdr.cdc.gov/. [Last accessed on 2019 Jan 10].
145. Rubin's pathology: Clinicopathologic foundations of medicine. Raphael Rubin R, Strayer DS. 5th ed. Pennsylvania, USA: Lippincott Williams and Wilkins (LWW); 2008.
146. Flora G, Gupta D, Tiwari A. Toxicity of lead: A review with recent updates. Interdiscip Toxicol 2012;5:47-58.
147. Wigle DT. Child Health and the Environment. New York, NY: Oxford University Press; 2003.
148. Froom P, Kristal-Boneh E, Benbassat J, Ashkanazi R, Ribak J. Predictive value of determinations of zinc protoporphyrin for increased blood lead concentrations. Clin Chem 1998;44:1283-8.
149. Arruda-Neto JD, de Oliveira MC, Sarkis JE, Bordini P, Manso-Guevara MV, Garcia F, *et al*. Study of environmental burden of lead in children using teeth as bioindicator. Environ Int 2009;35:614-8.
150. Lansdown R, Yule W. Lead Toxicity: History and Environmental Impact (The Johns Hopkins Series in Environmental Toxicology). Baltimore, MD: Johns Hopkins University Press; 1986.
151. Kosnett MJ, Wedeen RP, Rothenberg SJ, Hipkins KL, Materna BL, Schwartz BS, *et al*. Recommendations for medical management of adult lead exposure. Environ Health Perspect 2007;115:463-71.
152. Aliasgharpour M, Abbassi M. The absence of hematological outcome in workers occupationally exposed to lead in Tehran-Iran. Haema 2006;9:398-400.
153. Agency for Toxic Substances and Disease Registry (ASTDR), US. Toxicological Profile for Cadmium; 2012. Available from: https://www.atsdr.cdc.gov/. [Last accessed on 2019 Jan 12].
154. Liu J, Goyer RA, Waalkes MP. Toxic effects of metals. In: Klaassen CD, editor. Casarett and Doull's Toxicology: The Basic Science of Poisons. 7th ed. New York, NY: McGraw-Hill; 2008. p. 931-80.
155. Järup L, Hellström L, Alfvén T, Carlsson MD, Grubb A, Persson B, *et al*. Low level exposure to cadmium and early kidney damage: The OSCAR study. Occup Environ Med 2000;57:668-72.
156. Gallagher CM, Kovach JS, Meliker JR. Urinary cadmium

and osteoporosis in U.S. Women > or = 50 years of age: NHANES 1988-1994 and 1999-2004. Environ Health Perspect 2008;116:1338-43.
157. Satarug S, Moore MR. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. Environ Health Perspect 2004;112:1099-1103.
158. Agency for Toxic Substances and Disease Registry (ASTDR), US. Toxicological Profile for Mercury; 1999. Available from: https://www.atsdr.cdc.gov/. [Last accessed on 2019 Jan 12].
159. Muttera J, Curthb A, Naumann J. Does inorganic mercury play a role in Alzheimer's disease? A systematic review and an integrated molecular mechanism. J Alzheimers Dis 2010;22:357-74.
160. Caito SW, Jackson BP, Punshon T, Scrimale T, Grier A, Gill SR, *et al*. Editor's highlight: Variation in methylmercury metabolism and elimination status in humans following fish consumption. Toxicol Sci 2018;161:443-53.
161. Bjørklund G, Dadar M, Mutter J, Aaseth J. The toxicology of mercury: Current research and emerging trends. Environ Res 2017;159:545-54.
162. Alexandrov PN, Pogue AI, Lukiw WJ. Synergism in aluminum and mercury neurotoxicity. Integr Food Nutr Metab 2018;5:1-7.
163. Agency for Toxic Substances and Disease Registry (ASTDR), US. Toxicological Profile for Aluminum; 2008. Available from: https://www.atsdr.cdc.gov/. [Last accessed on 2019 Jan 18].
164. Klotz K, Weistenhöfer W, Neff F, Hartwig A, Thriel CA, Drexler H. The health effects of aluminum exposure. Dtsch Arztebl Int 2017;114:653-9.
165. Agency for Toxic Substances and Disease Registry (ASTDR), US. Health Consultation, blood and urine tests. U.S. Department of Health and Human Services. Services, Public Health Service, Centers for Disease Control. Atlanta, GA; 2004. Available from: https://www.atsdr.cdc.gov/HAC/pha/BloodUrineTestResults051104-FL/BloodUrineTestResultsHC051104. [Last accessed on 2019 Jan 18].
166. WHO fact sheet on Arsenic. 15 February 2018.
167. Quansah R, Armah FA, Essumang DK, Luginaah I, Clarke E, Marfoh K, *et al*. Association of arsenic with adverse pregnancy outcomes/infant mortality: A systematic review and meta-analysis. Environ Health Perspect 2015;123:412-21.
168. Farzan SF, Karagas MR, Chen Y. In utero and early life arsenic exposure in relation to long-term health and disease. Toxicol Appl Pharmacol 2013;272:384-90.
169. Tolins M, Ruchirawat M, Landrigan P. The developmental neurotoxicity of arsenic: Cognitive and behavioral consequences of early life exposure. Ann Glob Health 2014;80:303-14.
170. Agency for Toxic Substances and Disease Registry (ATSDR). Public health statement. Arsenic. CAS#:7440-38-2. August 2007.
171. Gielen M, Tiekink ER. Metallotherapeutic drugs and metal-based diagnostic agents. Wiley & Sons Ltd; 2005.
172. Zhou LY, Chen FY, Shen LJ, Wan HX, Zhong JH. Arsenic trioxide induces apoptosis in the THP1 cell line by down regulating EVI-1. Exp Ther Med 2014;8:85-90.
173. Wang S, Zhou M, Ouyang J, Geng Z, Wang Z. Tetraarsenictetrasulfide and arsenic trioxide exert synergistic effects on induction of apoptosis and differentiation in acute promyelocytic leukemia cells. PLoS One 2015;10:e0130343.
174. Ghaffari SH, Yousefi M, Dizaji MZ, Momeny M, Bashash D, Zekri A, *et al*. Arsenic trioxide induces apoptosis and incapacitates proliferation and invasive properties of U87MG glioblastoma cells through a Possible NF-κB-mediated mechanism. Asian Pac J Cancer Prev 2016;17:1553-64.
175. Sun XP, Zhang X, He C, Qiao H, Jiang X, Jiang H, *et al*. ABT-737 synergizes with arsenic trioxide to induce apoptosis of gastric carcinoma cells *in vitro* and *in vivo*. J Int Med Res 2012;40:1251-64.
176. Wang Y, Wang L, Yin C, An B, Hao Y, Wei T, *et al*. Arsenic trioxide inhibits breast cancer cell growth via microRNA-328/hERG pathway in MCF-7 cells. Mol Med Rep 2015;12:1233-8.
177. Walker AM, Stevens JJ, Ndebele K, Tchounwou PB. Evaluation of arsenic trioxide potential for lung cancer treatment: Assessment of apoptotic mechanisms and oxidative damage. J Cancer Sci Ther 2016;8:1-9.
178. Hu HT, Yao QJ, Meng YL, Li HL, Zhang H, Luo JP, *et al*. Arsenic trioxide intravenous infusion combined with transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with pulmonary metastasis: Long-term outcome analysis. J Gastroenterol Hepatol 2016;32:295-300.
179. Zhong LU, Xu F, Chen F. Arsenic trioxide induces the apoptosis and decreases NF-κB expression in lymphoma cell lines. Oncol Lett 2018;16:6267-74.
180. WHO. Hydrogen sulfide in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality. Geneva: World Health Organization; 2003.
181. Mahurpawar M. Effects of heavy metals on human health. Inter J Res – Granthaalayah 2015;3.
182. Agency for Toxic Substances and Disease Registry (ATSDR). Public health statement. Tin and tin compounds. 2005. Available from: https://www.atsdr.cdc.gov/. [Last accessed on 2019 Jan 20].
183. Winship KA. Toxicity of tin and its compounds. Adv Drug React Acute Poisoning Rev 1988;7:19-38.
184. The American Heritage Dictionary of the English Language, Fifth Edition: Fiftieth Anniversary Printing". hmhbooks.com. Houghton Mifflin Harcourt. Retrieved September 19, 2019.
185. Gitlin M. Lithium side effects and toxicity: Prevalence and management strategies. Int J Bipolar Disorder 2016;4:27.
186. Berk M, Cowdery S, Williams L, Malhi GS. Recalibrating the risks and benefits of lithium therapy. Br J Psychiatry 2017;211:1-2.
187. Malhi GS, Berk M. Is the safety of lithium no longer in the balance? Lancet 2012;379:690-2.
188. Kleiner J, Altshuler L, Hendrick V, Hersham JM. Lithium-induced subclinical hypothyroidism: Review of the literature and guidelines for treatment. J Clin Psychiatry 1999;60:249-55.
189. Bocchetta A, Cocco F, Velluzzi F, Del Zompo M, Mariotti S, Loviselli A. Fifteen year follow up of thyroid function in lithium patients. J Endocrinol Invest 2007;30:363-6.
190. Schwarz K. Essentiality versus toxicity of metals. In: Brown SS, editor. Clinical Chemistry and Chemical Toxicology of Metals. New York: Elsevier/North Holland; 1977. p. 3-22.
191. Baer L. Pharmacology – Lithium absorption, distribution, renal handling, and effect on body electrolytes. In: Gershon S, Shopsin B, editors. Lithium. Boston, MA: Springer; 1973. p. 33-49.