Review article

Trace Elements in Human Nutrition: A Review

Aliasgharpour Mehri ; Rahnamaye Farzami Marjan

1 *Ministry of Health & Medical Education- Tehran-Iran.*

Abstract

Trace elements also known as trace minerals, are the chemical components that naturally occur in soil, plant, and wildlife in minute concentrations. They are necessary for the optimal development and metabolic functioning such as proper cell metabolism, effective immune function, and healthy reproduction of humans . Their role and homeostasis in living organisms varies. There are 19 known trace elements that are categorized in three groups (WHO classification) ; essential elements ,probably essential elements, and potentially toxic elements .This review provides some detailed information and criteria for assessing the probable trace element status in human physiology . In addition, for some elements it may offer additional effective ways of diagnosis to physicians as well as interested peoples.

Key Words: *Trace Elements -Essential-Immune Function-Homeostasis-Organisms*

Corresponding Author : Mehri Aliasgharpour

Ministry of Health & Medical Education- Tehran Iran

m.asgharpour@ymail.com

Introduction.

Trace elements are dietary mineral that are in very minute quantities (less than 0.01%) of the mass of the organism. They are useful for proper growth , development, maintaining and recovering the health of the organism. They have several roles in living organisms. Some are essential components of enzymes where they attract substrate molecules and facilitate their conversion to specific end products. Some donate or accept electrons in reactions of reduction and oxidation, which results in the generation and utilization of metabolic energy. Some trace elements impart structural stability to important biological molecules. Finally, some trace elements control important biological processes through such actions as facilitating the binding of molecules to receptor sites on cell membranes, altering the structure or ionic nature of membranes to prevent or allow specific molecules to enter or leave a cell, and inducing gene expression resulting in the formation of proteins involved in life processes.

Homeostasis, the ability of the body to maintain the content of a specific substance such as a trace element within a certain range despite varying intakes, involves the processes of absorption, storage, and excretion. The relative importance of these three processes varies among the trace elements. The homeostatic regulation of trace elements existing as positively charged cations (for example, copper, zinc) occurs primarily during absorption from the gastrointestinal tract. Trace elements absorbed as negatively charged anions (for example, boron, selenium) are usually absorbed freely and completely from the gastrointestinal tract. Thus, they are homeostatically regulated primarily by excretion through the urine, bile, sweat, and breath. Storage of trace elements in inactive sites or forms is another mechanism that prevents inappropriate amounts of reactive trace elements to be present. Release of a trace element from a storage site also can be important in preventing deficiency. There are 19 trace elements that based on the nutritional significance have been divided into three groups (WHO classification):

1- *Essential elements such as iodine and zinc and etc.*

2- *Probably essential elements such as manganese and silicon and etc*

3- *Potentially toxic elements such as fluoride,lead,cadmium, mercury , & Lithium*.

1-Essential elements

Essential trace elements are required by man in amounts ranging from 50 ug to 18 mg per day. They are as catalytic or structural components of larger molecules. Researchers have identified 6 essential trace elements; Chromium, Copper, Zinc, Selenium, Molybdenum and Iodine that their function were previously unknown. Marginal or severe essential trace element imbalance can be considered risk factors for several diseases of public health importance, but proof of cause and effect relationships will depend on a more complete understanding of mechanisms of action, on better analytical procedures and functional tests to determine marginal trace element status in man [1].

Chromium

Chromium is the most important mineral for overweight people. In addition is one of the key minerals in controlling both blood sugar and fat levels. As the main component of Glucose Tolerance Factor (GFT) , chromium assists insulin in reducing blood glucose , by stimulating glucose uptake by the muscles and other tissues. When chromium levels are low, the circulating level of (GFT) is low , and insulin is then less effective in reducing blood sugar, therefore it remains high, stimulating further insulin release, which is still blocked from being effective . The perpetuation of this cycle, and its resultant effects are known as insulin resistance, the precondition leading to diabetes [2].

Short term symptoms of chromium deficiency are hypoglycemia and mood swing associated with rapid and large swings in blood glucose levels, especially after carbohydrate rich meals. Long term symptoms are those associated with diabetics, which is an almost inevitable consequence of chromium deficiency such as high blood pressure, heart disease, stroke and obesity .

Diets that are rich in refined carbohydrates , such as white flour, white pasta, white rice, potatoes and processed foods will use up chromium at a high rate and can be lead to deficiencies [3].

There are not sufficient evidence to set an estimated average requirement of chromium. Therefore, an adequate intake is based on estimated mean intakes. The adequate intake for young males is set at 35 >g/day, and that for young females is set at 25 >g/day. Some of the best food sources of chromium are whole grains, some vegetables (for example, broccoli and mushrooms), liver, processed meats, cereals, spices. egg yolks , beef, molasses, cheese, grape juice, whole wheat bread, honey, potatoes, chicken, spinach, bananas, carrots and blueberries.

Copper

Copper in its many form is the third most mineral in the body. In addition, to being important for many enzymes. Copper is found throughout the musculo-skeletal system, although the largest amount is found in the brain and liver. Copper is involved in the release of energy inside the cell and contributes to the function of many antioxidants thus mops up the free radicals that cause cell damage. The formation and regulation of hormones such as melatonin is under the control of copper ,via its role in the blood protein ceruloplasmin, responsible for the production of a wide range of neurotransmitters and other neuroactive compounds including the catecholamine's and encephalins. Furthermore, collagen production , formation of red blood cells and the oxidation of fatty acids are all highly dependent on copper concentration [1,4]. Copper is also required for the proper function of Vitamin C and iron absorption.

copper deficiency per se is rare. However, due to interaction with zinc, high zinc levels can prevent proper absorption of copper. Since both compete for the same absorption sites in the gut. Therefore, if there is an excess in one in the diet , the other will be likely deficient. Furthermore, nutritional copper deficiency is usually accompanied by a marked decline in plasma ceruloplasmin activity and an associated inhibition of iron release from the liver and other tissue. These changes reflect the role of ceruloplasmin as a ferroxidase [4].

Symptoms largely reflect the systems which utilize copper including collagen deficiency (poor bone and joint function as well as vascular disease). In addition, the involvement of copper in numerous hormonal systems means that those systems can be severely affected as a result of deficiency, which may lead to brain dysfunction and sometimes altered levels of red blood cells and cholesterol.

Lamb, liver, crab ,nuts, shrimps ,peanuts, chocolate ,olives, carrots garlic and tuna are good sources of copper. Many people wear copper bands to help them with inflammatory disease , such as arthritis. In this case the copper is absorbed through the skin. In fact, much of our dietary copper comes from copper pipes, utensils and cookware [1,4] .

Zinc

Zinc is one of the minerals one should never be without and has such a wide application in human health. It is necessary for a healthy immune system and is also important in fighting skin problems such as acne, and sore throats. It is further needed for cell division, hair, tissue, nails, skin and muscles growth. Children for normal growth and sexual development also require zinc. Furthermore, zinc helps to control oil glands, and is required for the synthesis of protein and collagen , which is needed for wound healing and a healthy skin.

The principle clinical features of severe zinc deficiency in human are growth retardation. It also will result in an under performing immune system, allergies, loss of smell and taste, falling hair, white spots under finger nails, skin problems , and sleep disturbance. The effects of marginal or mild zinc deficiency are less obvious and can readily be overlooked. A reduced growth rate and impaired resistance to infection are frequently the only manifestations of mild deficiency in humans.

Symptoms of toxicity occur in elevated zinc intakes (4-8 g) and It can actually harm the immune system instead of assisting it. In addition, Long term exposure to high zinc intakes substantially in excess of requirements has been shown to result in interference with the metabolism of other trace element. Copper utilization is especially sensitive to an excess of zinc [1,4] .

Interaction induced by high intakes of iron appears to be potentiated by increasing intakes of ascorbate. The adverse effects of zinc on iron absorption induced by iron: zinc ratio of 2:1 and is also made worse by decrease in dietary ascorbate when the dietary phytate content is high. Such result sugest that these antagonisms may depend not on total iron but on the proportion of iron present in oxidation or reduced forms. Iron dependent interactions and antagonisms are much more clearly evident when iron and other elements (e.g. copper, zinc) are administered in solution or in discrete doses rather than as supplements in solid diets [5] . However, in a multi-vitamin situation , it is necessary to note that zinc and iron is nearly in the same amounts [1,4] . Moreover, intake of zinc should be kept under 100 mg/day and large amounts may result in nausea, diarrhea, dizziness, drowsiness and hallucinations. Outstanding sources of zinc are found in red meat, poultry, fish, grains, nuts, eggs, and seeds. Green leafy vegetables and fruits are only modest sources of zinc because of their high water content.

Selenium

Selenium salts are toxic in large amounts, but trace amounts are necessary for cellular function in many organisms, including all animals. Early interest in the biological role of selenium centered on its action as a constituent of the antioxidant enzymes glutathione peroxides and thioredoxin reductase (which indirectly reduce certain oxidized molecules in animals and some plants). However, recent studies show that iodine and selenium metabolism are interrelated in the conversion of thyroxine to 3,5,3'-triiodothyronine by a selenium containing deiodinase enzymes**.**

The human body's content of selenium is believed to be in the 13–20 mg range. Dietary selenium comes from nuts, cereals, meat, mushrooms, fish, and eggs. Brazil nuts are the richest ordinary dietary source. In descending order of concentration, high levels are also found in kidney, tuna, crab, and lobster [6,7] .

Molybdenum

The most important role of molybdenum in living organisms is sharing a common cofactor , molybdoprotein, at the active site in certain enzymes. Molybdoprotein is bound on oxidized molybdenum atom through adjacent sulfur (or occasionally selenium) atoms. In human a process of purine catabolism, is catalyzed by xanthine oxidase, a molybdenum containing enzyme. The activity of xanthine oxidase is directly proportional to the amount of molybdenum in the body. However, an extremely high concentration of molybdenum reverses the trend and can act as an inhibitor in both purine catabolism and other processes. Molybdenum concentration also affect protein synthesis , metabolism and growth. Furthermore, high level of molybdenum can interfere with the body's uptake of copper, resulting in copper deficiency. It also prevents plasma proteins from binding to copper and increases the amount of copper that is excreted in urine.

Human body contains about 0.07 mg of molybdenum/kg of weight. The average daily intake of molybdenum varies between 0.12 and 0.24 mg, but it depends on the molybdenum content of the food. Pork, lamb, and beef liver each have approximately 1.5 parts per million of molybdenum. Other significant dietary sources include green beans, eggs, sunflower seeds, wheat flour, lentils, cucumbers and cereal grain. Acute toxicity has not been seen in humans, and the toxicity depends strongly on the chemical state [8,9,10] . Molybdenum concentration in the body is higher in the liver and kidneys and is lower in the vertebrate. Molybdenum is also present within human tooth enamel and may help prevent its decay [8,10,11] .

Iodine

The major role of iodine in nutrition arises from its important role played by thyroid hormones in regard to the growth and development of humans. The effects of iodine deficiency on growth and development are now denoted by the term iodine-deficiency disorders (IDD) that are seen at all stages of development, and particularly in the fetus, the neonate and the infants.

Iodine nutritional status can be assessed by means of goiter surveys, the determination of urinary iodine excretion, and the measurement of levels of thyroid hormones and of the pituitary thyroid stimulating hormone (TSH) [12] . Recommended dietary allowance (RDA) for adults is 150 >g/day. Iodized salt has been the major method for assuring adequate iodine intakes. Other sources of iodine are seafood and foods from plants grown on high-iodine soils.

2-Probably essential elements

Very little is known about these elements and they are thought unlikely to have a beneficial function in the life process of humans. They include manganese, silicon, nickel, boron, and vanadium.

Manganese

Manganese is an element that is only 0.00016% of the human body. It functions as both an activator and a constituent of several enzymes in the body. Manganese deficiency has been produced in many species of animals, but instances of nutritional deficiency in human subjects have not been unequivocally identified [13] .

Silicon

Silicon the second most abundant element in the earth's crust, is not found free in nature, but occurs as the oxide and silicates. It is found in greatly varying amounts in different plants, being present in the macro-quantity of about 1.2% in maize. While apparently unnecessary to man and not essential to all plant growth, it is valuable in giving mechanical strength to most plants. It is present especially in the connective tissue of mammals and forms a high proportion of the ash of feathers, probably giving them rigidity. In addition, the essential role of silicon in the development of bone in two species of experimental animals has been shown. However, no data are available from which human requirement for silicon can be estimated [14] .

Nickel

Nickel is not normally of biological interest except as causing toxicity. Between 8% and 50% of nickel ingested in drinking water after an overnight fast is absorbed by humans, resulting in marked hypernickelaemia in serum . Furthermore, contact dermatitis is the most important clinical effect of excessive nickel exposure .Because nickel deficiency has not been seen, status indications of a low intake of nickel have not received much attention [15-16] .

Boron

The finding that boron may be nutritionally important for human is so recent that there has been no opportunity to investigate possible indicators of an inadequate boron status.

The daily intake of boron by human can vary widely depending on the proportions of various food groups in the diet. Foods of plant origin, especially fruits ,leafy vegetables, nuts, and legumes are rich sources. Meat ,fish, and dairy products are poor sources.

The function of boron in mammalian tissues are unknown and its physiological roles and the pathological effects of boron deficiency should be investigated more fully with a view to assessing the nutritional significance of dietary boron [16] .

Vanadium

Vanadium is one of the less common elements and was certainly not regarded as being of biological significance. However, In mammals the element has beneficial effects on teeth, and it assists haemopoiesis. It also reduces cholesterol levels, a desirable factor in treating certain diseases, and some cancers are inhibited by it, but its compounds are very poisonous.

Daily dietary intake of vanadium is of the order of a few tens of ug and may vary widely. Only a few food items, including spinach, parsley, mushrooms, and oysters contain relatively large amounts of vanadium [17] .

3- Potentially toxic elements

Potentially Toxic Elements (PTEs), if present in excessive concentrations may be hazardous to health and/or inhibit plant growth. However, there may be some possibility with essential functions for these elements. In this category fluoride, lead, cadmium, and mercury are included.

Fluoride

Fluorine is only a minute part of the weight of man and enters the body as a variable constituent of both drinking water and foods. Body fluoride status depends on a multiplicity of factors, including the fluoride content of natural drinking water, the total amount ingested daily, the duration of ingestion and the efficiencies of intestinal absorption and renal excretion. The fluoride content of natural water may range from less than 0.1 mg/L to more than20mg/L .

A low level of fluorine in drinking water is linked to tooth decay. The dental tissue usually shows the earliest signs of toxicity ,and mottling of tooth enamel is a well known manifestation of excess fluoride ingested. Long term exposure to high levels of fluoride leads to dental destruction. Furthermore, in the body ionic fluoride rarely exists in blood, most ingested fluoride is trapped by bone tissue. In bone, fluoride accumulate in the lattice of bone crystal, where it stimulates new bone formation locally. Moreover, the blood concentration of fluoride increases from the value for normal blood fluoride of 0.04 ug/ml to values as high as 0.5-8.0 ug/ml, which have been reported in patients exhibiting clinical signs of fluorosis. Fluoride is also actively secreted in milk and human milk has been reported to contain 7ug of fluoride /liter when environmental fluoride was 1ug/ml in drinking water. This is a case of the need for the delicate balance between excess and the amount necessary to health [18,19] .

Biological interactions between fluoride and calcium are known to occur and severe clinical forms of fluoride toxicity are reported among population with poor calcium nutritional status [20] .

The fluoride intake in countries with high environmental temperature is high since there is high water consumption . This should be taken into account when deriving regionally applicable estimates for the safe upper limits of fluoride consumption from drinking water and the diet. Adult intakes exceeding 5 mg of fluoride per day from all sources probably pose a significant risk of skeletal fluorosis.

Lead, cadmium, and mercury

Apart from those communities exposed to high levels of pollution by industrial effluents or emission rich in heavy metals , for most individuals ,food and diet are the most important sources of these potentially toxic elements. At present most available data relate to the interaction of heavy metals with dietary macromolecules. For example, absorption of lead is substantially greater by fast subjects than by fed subjects. Of the many dietary interactions influencing lead uptake or retention those with calcium and iron are particularly important [21,22] .

The toxic effects of lead involve several organs. The nervous system of infants and children is particularly sensitive to lead toxicity [23] . Adults exposed occupationally or accidentally to excessively high levels exhibit peripheral neuropathology and chronic nephropathy. However, the critical or most sensitive effect for adults in the general population may be the development of hypertension [24] . Defects in hemoglobin synthesis and shortened erythrocyte life span provide biochemical indication of lead exposure in the absence of clinically detectable effects, but anemia in the absence of other effects attributable to such exposure is uncommon [24].

Cadmium

uptake is enhanced in elderly people with low body iron stores. In addition, health risks are greatest when inhalation of cadmium from occupational sources results directly in the lung damage. Cadmium retention in body tissues is related to the formation of cadmium metallothionein , a cadmium protein complex of low molecular weight. The synthesis of this protein is induced by the essential metals copper and zinc in liver and kidney, but also by cadmium, which may replace these metals or share the protein with them. Cadmium is present in most organs, but the highest concentration are found in kidney where it accumulates with age in proportion to the total body cadmium burden. In addition, the brain is the critical organ.

The most important measure of excessive exposure relates to increased cadmium excretion in urine . In populations not exposed to excessive cadmium, urinary cadmium excretion is small and relatively constant, usually 1 or 2 ug/day . In some cadmium workers, increase in urinary cadmium may not occur until all the available cadmium binding sites of metallothionein , are saturated [25] .

The toxicological features of **mercury** reflect in three forms : elemental, inorganic and organic compounds [25,26] . Inorganic compounds may contain mercury in oxidation states +1 or +2. A study on human volunteers indicated the gastrointestinal absorption of inorganic mercury compounds from food is less than 7%. Furthermore, Kidneys retain the greatest concentration of mercury following exposure to its inorganic compounds or vapor, whereas organic mercury has a greater affinity for the brain, and particularly the posterior cortex. However, mercury from vapor tends to accumulate in the central nervous system more readily than inorganic mercury compounds.

Current understanding of the metabolism of mercury is based on the results of experimental animal studies [26,27]. .All forms of mercury cross the placenta to the fetus. Fetal uptake of elemental mercury by rate is 10-40 times higher than uptake after exposure to inorganic compounds.

The biochemical indices of mercury toxicity are limited to measurements of mercury in body fluids and tissues and the monitoring of their relationship to clinical signs. The critical effect in adults is paraesthesia. It has been estimated that the average long term daily intake associated with adverse health effects in the most susceptible individual is 300 ug/day for an adult or 4.3 ug /kg of body weight per day. Execration of mercury in urine and feces varies with the form of mercury, size of dose and time after exposure [27] .

Aluminum

There are no substantiated evidence that aluminum has any essential function in animals or humans. The only main point is its potential toxicity if exposure is excessive. Dialysis encephalopathy in a large number of patients with renal failure undergoing chronic dialysis was shown to attribute to the high aluminum content of some water used for the preparation of dialysates [28] Aluminum levels in the brain and in other tissues of affected subjects were consistently elevated. Excess aluminum also affects the skeleton by markedly reducing bone formation, resulting in osteomalacia. A further pathological manifestation of aluminum toxicity is a microcytic hypochromic anemia not associated with iron deficiency. Such problems have practically disappeared since the use of aluminum-free deionized water for dialysis became routine. The toxicological aspects of orally consumed aluminum are less well defined. It is poorly absorbed from the intestines; the small amounts absorbed from normal diets are excreted by healthy kidneys, so that no accumulation occurs.

Aluminum interacts with a number of other elements, including calcium, fluorine, iron, magnesium, phosphorus and strontium and when ingested in excess, can reduce their absorption [29] . Because of this property, it has been used therapeutically to treat fluorosis and to reduce phosphorus absorption in uremic patients. Furthermore, there is no known risk to healthy people from typical dietary intakes of aluminum. Risks arise only in persons with impaired kidney function.

Arsenic

Arsenic occurs in the trivalent and pentavalent forms in foods, water and the environment. The main uses of arsenic is in agricultural chemicals, such as pesticides, herbicides, cotton desiccants, and wood preservatives. In addition, it is used as an additives to animal feeds, and as well as in pharmaceutical products ,all of which have a direct impact on the environment.

Although arsenic compounds are best known historically for their toxicity, their pharmacological action is also well documented. Furthermore, since experimental arsenic deficiency has been produced in four species, the element may have an essential function fulfilled by very low dietary arsenic intakes. The biological effects of arsenic depend markedly on the chemical form in which the element is presented, inorganic compounds being more toxic than the most organic ones. Most living organisms convert the former by methylation into a large variety of less toxic organic arsenic compounds ,which are then excreted [30] .

The major cause of concern with arsenic is the potential toxicity of its compounds to human. Acute poising , characterized by nausea, vomiting, diarrhea, and severe abdominal pain, is relatively rare. Chronic toxicity , on the other hand , is known to occur as a result of exposure to natural sources in some countries [29] or from accidental contamination of foods [29] . Consumption of water containing 0.8 mg of arsenic/L over extended periods of time and a dietary intake of approximately 3 mg of arsenic/day for 2-3 weeks have been identified as causes of arsenic intoxication. However, the toxicity of arsenic compounds depends greatly on their chemical nature that general estimates of safe intake can not be made with confidence. In conclusion, if a human requirement for arsenic does exist, it is probably close to 20 ug/day for adults and is easily met by most diets.

Tin

Tin has no known biochemical function. However, it could have a function in the tertiary structure of proteins or other biosubstances. In industry, organic tin compounds are used as catalysts for polymerization, and transesterification .

Signs of chronic exposure to excessive intake of inorganic tin include growth depression and anemia [31] . Tin toxicity also modifies the activities of several enzymes and it has been claimed that it interferes with the metabolism of zinc, copper, and calcium. As compared with inorganic tin, organic tin compounds are appreciably toxic and attack the central nervous system [32] . ·

Signs of tin deficiency in human have yet to be described. Instances of tin intoxication after oral ingestion are usually associated with elevated intakes through food contaminated by corrosion of tin lined cans. The conclusion reached in most studies to date is that the usual environmental exposure poses little threat of toxicity.

Lithium

Lithium salts have been used worldwide as an effective treatment for manic depressive episodes ever since their introduction [32] . Effective dosages 250-500 mg of lithium/day in an adult, require close monitoring, because the margin of safety is not wide and effects on the thyroid and excessive weight gains are not uncommon. Lithium affects many metabolic pathways and organ functions at therapeutic and toxic intakes, but its basic function and mode of action are still unknown [33,34,35] .

Conclusion

In closing, as we view the importance of trace elements in living organisms, detailed studies indicate a fine balance must be obtained in trace elements concentration in order to secure health and even to maintain life in living organisms. However, there is danger of over dose, most elements in excess of certain limits of concentration have toxic effects. Trace elements may also act against each other, and in a few cases one may assist another. It is, however, most exceptional for one to be able to replace another.

References

1. Nguta J. Essential trace elements: trace elements in human and animal health. LAP Lambert Academic Publishing, 2010.

2. Offenbacher FG, Pi-Sunyer FX. Chromium in human nutrition. Annual review of nutrition.1988;8:543-563

3. Stoecker BJ. Chromium. In: Brown ML, ed. Present knowledge in nutrition, Washington, DC, International Life Science Institute.1990;287-293.

4. Chan s. Gerson B. Subramaniam S. The role of copper, molybdenum, selenium, and zinc in nutrition and health. Clin Lab Med 1998; Dec18(4):673-85.

5. Sandstrom B. Effects of inorganic iron on the absorption of zinc from a test solution and a composite meal. In: Mills CF, Bremner L, Chesters JK, eds. Trace elements in man and animals-TEMA.S. Farnham Royal, CAB International ,1985:414-416.

6. Selenium. Geneva, World Health Organization.1987 (Environmental Health Criteria 58).

7. Rayman MP. Selenium and human health. Lancet 2012;379 (9822):1256-68.

8. Rajagopalan KV. Molybdenum. In: Frienden E, ed. Biochemistry of the essential ultra trace elements. New York,, Plenum Press 1984; 147-174.

9. Curzon, M. E. J.; Kubota, J.; Bibby, B.G. . "Environmental Effects of Molybdenum on Caries" (PDF). Journal of Dental Research 1971; 50 (1): 74–77. doi:10.1177/00220345710500013401. http://jdr.sagepub.com/content/50/1/74.full.pdf.

10. Emsley, John . Nature's Building Blocks. Oxford: Oxford University Press.2001 ; 262–266. ISBN 0-19-850341-5.Avalable at: http://books.google.com/?id=j-Xu07p3cKwC&pg=PA265.

11. Coughlan, M. P. "The role of molybdenum in human biology". Journal of Inherited Metabolic Disease 1983; 6: 70–77.

12. Hetzal BS, Potter BJ, Dulberg EM. The iodine deficiency disorders: nature, pathogenesis and epidemiology. World review of nutrition and diet 1990; 62:59-119.

13. Friedman BJ, Jeanne H Freeland-Graves, Connie WB, Fares Behmardi, Roseann L Shorey-Kutschke, Richard AW, et al. Manganese balance and clinical observation in young men fed a manganese deficient diet. J nutrition 1987; 117:133-143.

14. Carlisle EM. Silicon: a possible factor in bone calcification. Science 1970; 167:279-280.

15. Smart GA, Sherlock JC. Nickel in foods and the diet. Food additives and contaminants 1987; 4:61-71.

16. Nielsen FH. The ultra trace elements. In: Smith KT, ed. Trace minerals in foods. New York, Marcel Dekker. 1988; 357-428.

17. Byrne AR, Kosta L. Vanadium in foods and in human body fluids and tissues .Science of the total environment 1978; 10:17-30.

18. Spak CJ,Hardell LI, DeChateau P. In: Mertz W,ed. Trace elements in human nutrition,5th ed,Vol.1. San Diego, Academic Press 1987;374.

19. Magalhães AC, Wiegand A, Rios D, Buzalaf MA, Lussi A. Fluoride in dental erosion. Monogr Oral Sci. 2011; 22:158-70.

20. Nuissinyaiou BS, Krishnamachari KAVR, Vijayasarathy C. ^{47}Ca turnover in endemic fluorosis and endemic genu valgum. British J Nutr 1979; 41:7-14.

21. Air quality criteria for lead. Research Triangle Park, NC, US Environmental Protection Agency. 1986; (report NO.EPA-6008-83/028cF).

22. Rabinowitz MB, Kopple JD, Wcrherill GW. Effect of food intake and fasting on gastrointestinal lead absorption in human. American J Clin Nutr 1980; 33:1784-1788.

23. Needleman HL, Gatsonis CA. Low level lead exposure and the IQ of children. A meta analysis of modern studies. J American Med Ass 1990; 263:673-678.

24. Tyroler HA. Epidemiology of hypertension as a public health problem: an overview as background for evaluation of blood lead – blood pressure relationship. Environmental health perspectives 1988;78:3-7.

25. Therenod F, Lee WK. Toxicology of cadmium and its

damage to mammalian organs. Met ions life Sci. 2013;11:415-90.

26. Methylmercury .Geneva, World health Organization.1990; 144 (Environmental Health Criteria 101).

27. Berlin M. Mercury. In: Friberg L, Nordberg GF, Vouk VB, eds. Handbook on the toxicology of metals ,2nd ed. New York, Elsevier/North Holland.1986;387-445.

28. Alfrey AC. Aluminum. In: Merrz W, ed. Trace elements in human and animal nutrition, 5th ed, Vol.2. Orlando, FL, Academic Press. 1986;.399-413.

29. Lotz M. Zisman E. Bartter FC. Evidence for a phosphorus-depletion syndrome in man. New England J Med.1968; 278:409-415.

30. Hughes MF, Beck BD, Chen Y, Lewis AS, Thomas DJ. Arsenic exposure and toxicology: a historical perspective. Toxicol Sci. 2011 ;123(2):305-32

31. Winship KA. Toxicology of tin and its compounds. Adverse Drug React Acute Poisoning. Rev 1988.7(1)19-38.

32. Piver WT. Organo tin compounds: industrial applications and biological investigation. Environment health perspectives.1973;4:61-79.

33. Cade JFJ. Lithium salts in the treatment of psychotic excitement. Med JAustralia 1949;2:349.

34. Schou M. Possible mechanism of action of lithium salts approaches and perspectives. Biochemical Society transactions1973;1:81.

35. Aliasgharpour M, Abbassi M, Shafaroodi H, Razi F. Subclinical hypothyroidism in lithium-treated psychiatric patients in Tehran, Islamic Republic of Iran. East Mediterr Health J. 2005; 11(3):329-33.