# Essential Trace Elements

Subjects: Others

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Trace elements produce double-edged effects on the lives of animals and particularly of humans. On one hand, these elements represent potentially toxic agents; on the other hand, they are essentially needed to support growth and development and confer protection against disease. The amount taken up and the accumulation in human tissues decisively control whether the exerted effects are toxic or beneficial. This entry provides a brief description of some toxic, likely essential and essential elements and their influence on human health.

Trace Elements | Potentially Toxic Elements | Likely Essential Elements | Essential Elements | Lead | Cadmium | Barium | Mercury | Zinc | Copper

## 1. Trace Elements

Trace elements are present in the human body in extremely small quantities of less than 0.01%. They are important for growth, development, maintenance and the recovery of health. They have various roles: some of them are essential components of enzymes, where they attract substrate molecules and facilitate their conversion into final products; others donate or accept electrons in the oxidation–reduction reactions necessary for the production and use of energy in the metabolism; others provide structural stability to some important biological molecules. Finally, some trace elements control important biological processes facilitating the binding of molecules to their receptors on the cell membrane, altering the structure or ionic nature of the membranes to regulate the access of certain molecules into the cell and inducing the expression of genes encoding for proteins involved in various vital processes.

Several studies report evidence of the possible involvement of trace elements in processes leading to an autoimmune response. For example, the causal relationship between mercury and immune diseases is well established and the mechanism has been hypothesized [1].

It has been discovered that mercury, nickel, cadmium, lead, aluminum and arsenic can exert immunotoxic effects through epigenetic mechanisms such as DNA methylation, post-translational modification of histones and miRNAs [2][3]. Furthermore, mercury, a possible risk factor for SLE, has been shown to induce the formation of anti-nuclear antibodies (ANA), hallmark of many autoimmune diseases, in mice [4].

The immunological effects of trace elements include immunomodulation, autoimmunity and allergy. These elements can act as immunosuppressants or as immune adjuvants. Their effects depend on the dose. In fact, their accumulation or deficiency can stimulate an alternative path that could induce the onset of disease. For example,

low zinc levels and high levels of copper, manganese and iron participate in the activation of inflammatory responses and responses to oxidative stress induced by the ROS and RNS [5].

Interactions between different oligoelements may play an important role in metabolic disease onset. For example, copper deficiency anemia can develop in people who consume high doses of zinc over a long period of time [6]. Other interactions include the ability of selenium to reduce the toxicity of methylmercury, cadmium [7] and trivalent, pentavalent inorganic arsenic through the formation of a conjugated As-Se-glutathyl excreted with bile [8]. In vitro and in vivo studies have shown that small initial doses of cadmium are protective against subsequent high doses of cadmium [9][10]. In fact, cadmium induces the synthesis and storage of low molecular weight proteins (metallothioneins) in the liver and kidneys. Metallothioneins, which are rich in sulfur-containing amino acids, can bind to subsequent doses of mercury or cadmium, thus decreasing their toxicity [9]. High dietary intakes of calcium and magnesium can have a beneficial effect by reducing the gastrointestinal absorption of lead. However, calcium can also reduce the absorption of iron and zinc. Molybdenum can reduce copper retention [11].

The storage of trace elements in non-metabolically active sites or forms is another mechanism that allows the accumulation of elements at dangerous concentrations.

Furthermore, releasing trace elements from a storage site can play an important role in preventing deficiencies. In fact, current evidence suggests that the low affinity copper transporter (CTR2), located in the membranes of intracellular organelles, could serve to release copper from lysosomal deposits or from other vesicles towards intracellular spaces [12]. Similarly, zinc efflux transporters in the Golgi membranes and in the cell membrane play an important role in the homeostatic regulation of the element [12].

The World Health Organization (WHO) [13] classified trace elements into three groups based on their possible nutritional roles:

- potentially toxic elements, e.g., lead (Pb), cadmium (Cd), fluorine (F), mercury (Hg), arsenic (As), aluminum (Al), barium (Ba), lithium (Li), tin (Sn);
- elements of probable physiological importance, e.g., manganese (Mn), silicon (Si), nickel (Ni), boron (B), vanadium (V);
- essential elements, e.g., chromium (Cr), copper (Cu), zinc (Zn), selenium (Se), molybdenum (Mb), cobalt (Co), iodine (I).

The elements mentioned are introduced mainly with food.

## 1.1 Potentially Toxic Elements

### 1.1.1 Lead

Lead (Pb) is one of the most important toxic elements. It has been used for decades for many technological processes, including the production of paints, gasoline and aviation fuel. The previous use of carbonate and oxide lead in these products represents the main source of exposure to this metal that is not degradable and remains in the environment as dust, in the soil and paint in old houses.

Lead toxicity is based on molecular mimicry with cellular cations and the formation of ROS. It replaces zinc and calcium in proteins involved in different biological processes, consequently altering protein structure and function [14].

Lead passes through the placenta, determining an increase in the blood levels of the fetus nearly identical to that in the maternal blood [15]. Lead toxicity affects almost every organ in the body, but the central nervous system is particularly sensitive to lead effects in both children and adults. Learning deficits and behavioral problems are serious effects of lead poisoning in children, while in adults, neuropathies, chronic nephropathies, anemia, hypertension and toxicity related to the reproductive organs are of particular importance [16]. Another target of lead toxicity is the immune system. According to Fenga et al. (2017), lead enhances Th2 cell development, affecting Th1 cell proliferation and leading to high levels of IgE and inflammatory cytokines [17]. However, other authors have demonstrated that there are not changes in cytokine levels related to the Th1-, Th2- and Th17-mediated immune responses after short-term exposure to lead, in contrast to chronic exposure [18]. Therefore, lead alters Th cell functions, increasing the susceptibility to autoimmune diseases and hypersensitivity. For example, one study found a positive correlation between exposure to absorbable lead in soil and MS prevalence in Iran [19].

### 1.1.2 Cadmium

Cadmium (Cd) is a toxic transition metal. Its industrial use was irrelevant up until 50 years ago. About 75% of the cadmium produced is used in batteries. It is also used as a pigment in paints and as a stabilizer in plastics. A potential source of cadmium is represented by the extraction of zinc and lead in mines, where lead is a secondary product. The natural presence of cadmium in zinc and lead deposits is well known.

The primary source of cadmium exposure is food, particularly cereals, leafy fruits and vegetables, crustaceans and liver and kidneys of animals, as well as contaminated drinks and cigarette smoke. Cadmium transplacental passage is not easy; however, since the absorption of micronutrients increases in pregnancy, cadmium absorption increases and accumulates at high concentrations. Cadmium exposure has been associated with nephrotoxicity, hepatotoxicity and effects on the immune system, bones and male reproductive physiology.

Several studies have shown that cadmium is an immunomodulator. It stimulates the production of Th2 cells. Stimulated macrophages and monocytes respond with the release of ROS and TNF α and production of the inducible nitric oxide (NO) enzyme synthase. Nitrogen oxides are known to regulate the proliferative response of lymphocytes [7]. Cadmium has been shown to inhibit glutathione reductase enzymes, implicated in the defense

against free radicals, and the enzyme thioredoxin reductase, an oxidoreductase that reduces protein thiols and has an important role in regulating the redox state of cells [20]. Furthermore, an in vitro study has shown that low doses of cadmium stimulate the immune system, while higher concentrations inhibit immune responses [21]. This could be in agreement with the results of an Iranian study in which a high concentration of absorbable cadmium in the soil was associated with a lower prevalence of MS [19].

### 1.1.3 Barium

Barium (Ba) constitutes about 0.05% of the Earth's crust. Exposure to this element deserves particular attention because it is commonly found in surface waters and can be released into the environment by the natural breakdown of rocks and minerals or as polluting waste from industry and human activities.

The toxicity of barium-containing compounds depends on solubility, i.e., soluble salts are more toxic than insoluble salts because they can be absorbed through the skin or inhaled. A US study reported the presence of 10 ppm (parts per million) of barium in wheat and corn crops; milk, potatoes and flour were the main sources of barium in the American diet [22].

The mechanism of action of Ba involves blocking $K^+$ efflux channels in the cell membrane, with a consequent increase in intracellular K+ levels and extracellular hypokalemia [23].

It can have an effect on skeletal muscles, smooth muscle and myocardial excitability and can lead to secondary respiratory paralysis and heart disease.

Although barium is found in low concentrations in the environment, the health consequences of chronic exposure have yet to be analyzed. A correlation study between geochemical data in Europe and the incidence of MS and T1D found a positive correlation between barium and sodium oxide present in soil and river sediments and these autoimmune diseases [24].

### 1.1.4 Lithium

Lithium (Li) is a moderately abundant alkaline metal present in the Earth's crust in an amount equal to 20 ppm. Lithium is easily absorbed by plants and its quantity varies widely, reaching 30 ppm in some cases. It is used for the production of alkaline batteries, soaps and large refrigeration and air conditioning systems. Lithium carbonate is used as an effective drug for the treatment of bipolar disorder.

Lithium can be absorbed by the inhalation of its aerosol and by ingestion. It was shown that treatment with lithium reduced MS symptoms in MS mouse models [25].

### 1.1.5 Mercury

Mercury (Hg) is found in rocks in the Earth's crust and occurs in coal and other fossil fuels. It is a common environmental pollutant. The most common sources of exposure are the consumption of fish and shellfish

contaminated with methylmercury and the inhalation of mercury vapors in industrial environments—for example, during the preparation of dental amalgam [26].

The immunotoxic effects of mercury have been observed in humans and animal models. It has been shown that subtoxic doses of mercury may induce a systemic autoimmune syndrome in mouse models [27]. Low doses of mercury and methylmercury cause immunosuppression, reducing Th1 responses and increasing those of Th2 [28] [29].

It has been suggested that mercury may have a role in accelerating or aggravating pre-existing systemic autoimmune conditions [30].

## 1.2 Likely Essential Elements

### Silicon

Silicon (Si) is a very abundant element in the Earth's crust, second only to oxygen, making up about 28% of the Earth's weight. It is not found in nature in its free state but in the form of oxides and silicates. Small quantities (1–10 ppm) of silica and silicates dissolved or in colloidal suspensions are present in surface waters. It is possible to find silicon at different concentrations in various species of plants; for example, it is detectable at concentrations close to 1.2% in *Zea mays*.

In vivo studies have shown lipid peroxidation, oxidative stress, an increase in IgM, serum IgG and the presence of ANA in mice exposed to silica, supporting its role as an adjuvant of T lymphocytes and as a possible factor triggering autoimmune diseases such as SLE and glomerulonephritis [31].

An association between systemic immune diseases and occupational exposure to silica dust has been observed [32]. Silica-derived polymers such as silicone elastomer have been increasingly recognized as potential inducers of autoimmune and autoinflammatory (linked to innate immunity stimulation) syndromes [33][34].

## 1.3 Essential Elements

### 1.3.1 Zinc

Zinc (Zn) is an essential trace element, ubiquitous in the environment and widely distributed in the body.

The dietary requirement for zinc is between 6.2 and 10.2 mg/day for women, between 7.5 and 12.7 mg/day for men and between 2.4 and 11.8 mg/day for children [35]. Rich sources of Zn in the diet are meat, milk, legumes, eggs, fish and cereals. Phytates (present in legumes, nuts and seeds), calcium and phosphates reduce zinc absorption. On the other hand, amino acids, picolinic acid and prostaglandin E2 can increase its absorption. Zinc needs increase up to two times during pregnancy and breastfeeding. In fact, zinc is lost in quantities of up to 2 mg per day until to 2 months after childbirth. Additionally, preterm infants require higher zinc levels due to inadequate deposits, reduced intestinal absorption and increased metabolic rate.

It has been observed that the fraction of zinc absorbed progressively decreases as zinc intake increases. This is due to the fact that Zn is an effective inducer of metallothionein synthesis, and when metallothionein in the intestinal cells is saturated, the absorption of Zn is reduced [35].

Zinc is predominantly found in muscles, bones, skin/hair, the liver and the pancreas. About 99% of zinc is intracellular and is distributed in the cytoplasm (50%), in the nucleus (30–40%) and in the cell membrane (10%), while the rest (about 1 mg/L) is bound to albumin in plasma (60–80%) [5].

Zinc is involved in a wide range of vital catalytic, structural and regulatory physiological processes and is required by more than 300 enzymes for their catalytic activation. It is involved in DNA, RNA and protein syntheses and is the cofactor of several transcription factors modulating the expression of zinc sensitive genes [36]. Furthermore, Zn binds to over 2500 proteins, maintaining their structural integrity and regulating their functions. It is one of the cofactors of the enzyme Cu/Zn superoxide dismutase (SOD), which plays a fundamental role in the removal of ROS and reduction of lipid peroxidation.

Zinc also plays an immune, anti-inflammatory and antioxidant role. It mediates innate immunity and influences acquired immunity by activating T lymphocytes and regulating the production of Th1 cytokines, B lymphocytes and antibodies. It is also used by macrophages for phagocytosis and cytokine production [36].

A recent meta-analysis has shown that low levels of zinchemia (in serum and plasma) are often observed in patients with autoimmune diseases [37]. Low zinc levels are known to contribute to immune defects associated with malnutrition [38]. In particular, a systemic zinc deficiency is associated with inflammation states, producing effects on the immune system. Interestingly, experiments conducted on cells, synoviocytes isolated from rheumatoid arthritis patients, have shown that the production of inflammation mediated cytokines IL-17/TNF in turn stimulates zinc uptake by the synoviocytes, thus increasing even more the inflammation, in a feedback loop between inflammation and zinc uptake [39].

As previously reported, Zn reduces the generation of ROS involved in the activation of NF-kB, a modulator of the immune response to infections whose dysfunction can cause autoimmune diseases and tumors. NF-kB inhibition results in the reduced generation of inflammatory cytokines and adhesion molecules [5].

Zinc deficiency induces thymic atrophy and reduces the activity of serum thymulin, a thymic zinc-dependent hormone necessary for the maturation and differentiation of T helper lymphocytes. The result is a decrease in Th1 cytokines, with a shift in activity towards Th2 lymphocytes and a reduction in the activity of natural-killer (NK) and cytotoxic T cells. Therefore, Zn deficiency induces an imbalance between Th1 and Th2 cell functions and between Treg lymphocytes and pro-inflammatory T cells, as well as the induction of Th17 lymphocyte activity, the main mechanisms that contribute to autoimmune disease pathogenesis. [5]. The proliferation of pre-activated human T cells and Th1/Th2/Th17 cytokine production may be suppressed by zinc aspartate [40].

A study has shown that the addition of Zn, in combination with probiotic complex and coenzyme Q1, to the diet of an animal model of arthritis suppressed the differentiation of Th17 lymphocytes [41]. Another study demonstrated that Zn suppressed Th17 development by inhibiting STAT3 activation in a mouse model of rheumatoid arthritis [42]. Zinc also induces a variety of other proinflammatory responses in T cells and B cells [43][44][45].

Studies in Sardinia and Sweden have shown that low concentrations of Zn in soils and drinking water were associated with a higher risk of T1D, suggesting that this metal has a protective role [46].

### 1.3.2 Copper

Copper (Cu) is the third most abundant essential trace element in the human body, after iron and zinc, constituting 75–100 mg of the total quantity. The dietary requirements for copper are 1.6 mg/day for men, 1.3 mg/day for women and 1 mg/day for children [47].

Cu is widely distributed in nature and is found at a concentration of about 55 ppm in the Earth's crust (77). It is almost always found in the form of minerals, such as sulphides, oxides, carbonates, silicates or, more rarely, in their native states. The most abundant minerals are copper and iron sulphides (chalcopyrite).

Food, drinks and water are the main source of exposure of the population to copper sulphate. Copper is contained in greater quantities in meat, liver and kidneys, in cereals, mollusks and in some fruits (avocado, walnuts, hazelnuts and dried grapes).

Copper exists in two oxidation states, as Cu (I) or Cu (II), and this ability to gain or lose an electron is at the basis of its role in the energy transfer processes in biological systems and in cellular respiration.

Many enzymes require copper as a cofactor, particularly those involved in iron metabolism, in the synthesis of neurotransmitters, in energy metabolism and in the cross-linking of collagen and elastin.

Copper deficiency symptoms have been observed in a X-linked recessive disease due to mutations of the copper transporter ATP7A. They include anemia, hypercholesterolaemia, metabolic syndrome, reduced glucose tolerance, hypopigmentation of the skin and hair, leukopenia, neutropenia, myelodysplasia and, in most patients, neurological effects, most commonly due to neuromyelopathy [48][49]. It has been hypothesized that anemia associated with copper deficiency is due to defective iron mobilization, resulting from reduced ceruloplasmin activity [49]. This enzyme, with its ferroxidase action, is fundamental for the transformation of $Fe^{2+}$ to $Fe^{3+}$, an indispensable step for the incorporation of iron into the circulating transferrin to avoid the toxicity of the free metal involved in the production of free radicals. Furthermore, copper deficiency has been associated with changes in immune and bone function. In particular, a reduced number of leukocytes and neutrophils and reduced antioxidant activity of Cu/Zn SOD, as well as the presence of lipid peroxidation, have been detected [48].

Since copper is involved in the synthesis of the myelin sheath, its deficiency can potentially cause myelopathy [50]. Moreover, copper has a regulatory role in cell growth and in maintaining homeostasis in the immune system. In

particular copper sulphate seems to exert beneficial effects in T1D mouse models, both by directly reducing the amount of free radicals and by lowering blood glucose levels [51].

### 1.3.3 Chromium

Chromium (Cr) is an essential nutrient involved in protein, lipid and carbohydrate metabolism. The dietary requirement for chromium is 20–35 µg/day [52]. Chromium is naturally present in trivalent, Cr (III), and hexavalent, Cr (VI), forms. Cr (VI) has been extensively used in the paint, steel manufacturing and leather industries. The association between Cr (VI) toxicity and lung cancer in stainless workers is well established [53]. Moreover, it has been demonstrated that Cr (VI) induces oxidative stress by increasing the production of ROS [54].

On the other hand, Cr (III) salts have been shown to possess beneficial effects as nutritional supplements in animals and humans [55].

Chromium deficiency has been observed in diabetic patients receiving chronic total parenteral nutrition. Chromium supplementation resulted in improved glucose tolerance [56].

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