

Essential and Toxic Trace Elements in Human Health and Disease: An Update

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ULTRATRACE ELEMENTS OF POSSIBLE IMPORTANCE FOR HUMAN HEALTH: AN UPDATE

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INTRODUCTION

Ultratrace elements are those elements with an estimated dietary requirement usually less than 1 mcg/g and often less than 50 ng/g diet for laboratory animals. Elements suggested to fit in the ultratrace category include arsenic, boron, bromine, cadmium, chromium, fluorine, lead, lithium, molybdenum, nickel, selenium, silicon, tin and vanadium. Since the first meeting in 1986 of the International Society of Trace Element Research in Humans (ISTEPH), an **increasing number of reports have appeared which describe findings that suggest several of the ultratrace elements are more important in human nutrition than currently acknowledged.**

Generally, these findings have come from studies in which specific trace element deficiencies have been examined in humans and experimental animals under some form of nutritional, metabolic, hormonal or physiologic stress. In other words, **the need for some ultratrace elements became apparent when organisms were stressed in some way that enhanced the need or interfered with the utilization of those elements.** Perhaps the best known demonstration of the use of this method to establish the nutritional importance of an ultratrace element was with selenium.

Ultratrace minerals is a term often applied to elements for which there is experimental evidence from animal models suggesting that they are essential for humans. However, the nutritional importance of these minerals has not been clearly established. One reason for the difficulty in establishing importance of ultratrace minerals is that they are required in such small amounts, 1 mg/day or less.

Since the early 1970s, there has been speculation that the lack of one or more of the ultratrace elements would be found responsible for some human diseases, such as atherosclerosis, osteoporosis and hypertension, with out complete understanding as to their cause. However, convincing evidence that ultratrace element deficiencies result in susceptibility to specific disorders has been elusive. A possible explanation for this elusiveness is that previous experimental approaches were too simplistic. They usually involved a search for a simple deficiency that was unlikely to be found due to the powerful homeostatic mechanisms of the body.

When an organism is exposed to some form of nutritional, metabolic, hormonal or physiologic stress, some ultratrace elements may be of nutritional significance. In other words, the **insufficient intake of a specific ultratrace element probably becomes apparent only when the body is stressed in some manner so as to enhance the need or interfere with the utilization of that element.** Examining 'the possibility that some of the ultratrace elements are of importance for humans exposed to various stressors has revealed that boron and silicon are candidates of potential nutritional concern. **The need for these minerals seems to be enhanced by human stresses, i.e., low dietary calcium and magnesium intakes or high dietary aluminum intake.**

At present, only seven trace elements have defined essential functions in humans. These elements are cobalt, copper, iodine, iron, molybdenum, selenium, and zinc. Essential functions have been identified for manganese in animals, but not in humans. Signs of chromium deficiency have been described for humans, but a specific biochemical role for chromium has not been demonstrated to satisfy orthodox science. A number of other elements in addition to the aforementioned nine elements have been suggested to be essential nutrients, including arsenic, boron, bromine, cadmium, fluorine, lead, lithium, nickel, silicon, tin, and vanadium. Deficiencies of only four elements--cobalt as vitamin B12, iodine, iron, and zinc--occur with known sufficient frequency in humans to be of concern to health professionals. Nonetheless, the trace elements are often suspected of being the missing link in some of the unexplained human diseases, such as atherosclerosis, osteoporosis, osteoarthritis, hypertension, and ischemic heart disease. Efforts to demonstrate that trace element deficiencies are the missing links generally have been unsuccessful. In the following, it is suggested that perhaps some of the failures have occurred because the experimental approach has not been correct in the past. Recent studies examining the need for various trace elements by animals under some form of nutritional, metabolic, hormonal, or physiologic stress have indicated that these are situations in which some of the trace elements may be of nutritional significance.

Factors Affecting Trace Element Requirements

Although trace elements play key roles in a variety of processes necessary for life, the occurrence of overt simple or uncomplicated deficiencies of any of the trace elements is probably relatively uncommon because of powerful homeostatic mechanisms that the human body possesses. However, **there are situations that may make a trace element nutritionally significant.** These include:

- Inborn (genetic) **error of metabolism** that affects absorption, retention, or excretion
- Alterations in metabolism and/or biochemistry as a secondary consequence to **malnutrition, disease, injury, or stress**
- Marginal deficiencies (slight deviation from an optimal intake of an essential nutrient) induced by various dietary manipulations or by direct or indirect **interaction with another nutrient or drug** and
- The **enhanced requirement** for a trace element caused by a sudden or severe change in the system requiring that element.
- Slow, cumulative effects of **continuous deficiency over time**

The preceding probably can be summarized by the statement that the insufficient intake of a specific trace element becomes obvious only when the body is stressed in some way that enhances the need, or interferes with the utilization, of that element.

Recently, Tapp and Natelson (1) presented the formula:

$$\text{Pathological Effects} = \text{Stress} \times \text{Organic Vulnerability}$$

This formula seems quite applicable to trace element nutrition. In other words, pathological effects are not likely to be seen if a trace element deficiency (organic vulnerability) is not multiplied by some significant stress. Likewise, pathological effects are not likely to be large if an organic vulnerability or an inappropriate lack of a trace element does not accompany stress. However, **the multiplication of a suboptimal intake of specific trace elements multiplied times the presence of some nutritional, metabolic, hormonal, or physiologic stress affected by that element most likely would lead to serious pathological consequences.** The preceding concept is supported by findings with selenium.

Selenium was first shown to be nutritionally important by using vitamin E-deficient animals. Close examination of published data indicates that a very limited number of deficiency signs are caused exclusively by selenium deficiency; most signs appear when vitamin E or antioxidant metabolism is suboptimal. Human diseases involving selenium apparently are not simple selenium deficiencies. For example, it has been suggested that Keshan disease, which responds to selenium supplementation, also involves another factor. Suggested possibilities include various toxins, hypoxia, or infectious agents, particularly viruses.

Examining the possibility that other trace elements are important in human nutrition in a manner similar to selenium has revealed several candidates of potential nutritional concern, including boron, chromium, copper, molybdenum, nickel, arsenic, silicon, and vanadium. This is especially true for boron and copper, which will be discussed most extensively here.

HOW SMALL IS A PART-PER-MILLION (PPM)?

Conversion Table

Unit Equivalent Equivalent

gram 1000 milligrams 1000 PPM

milligram 1000 micrograms 1 PPM

microgram PPB --

Assume a pinch of salt is about the size of a drop of water. Sixteen drops make 1 milliliter (ml); 30 ml make about 1 ounce; 32 ounces make 1 quart; and 4 quarts make 1 gallon. So a gallon contains a little more than 61,000 drops of water, and a single drop would be 1 part per million in about 16 gallons of water.

This may seem insignificantly small, but some minerals at such concentrations in plants, animals and humans are absolutely essential to life.

Chromium, cobalt, manganese, molybdenum, and nickel--all essential to human life--are found in the body in concentrations of parts per million.

Minerals originate in soil and water. Essential minerals can be depleted by intensive cultivation of a single crop year after year. On the other hand, overfertilizing can kill microorganisms needed to make soil minerals soluble for crop uptake or alter the chemical composition of the soil so that certain minerals become insoluble and cannot be taken up readily. Soils may be naturally deficient in cobalt, copper, molybdenum and phosphorus; other soils contain excessive amounts of selenium, yielding high-selenium grains and forage. Water supplies contain minerals. "Hard" water contains calcium, magnesium and sometimes iron and fluoride, and "soft" water contains more sodium and potassium and less calcium, magnesium and iron. Drinking water can sometimes provide small amounts of minerals.

WATER-SOLUBLE vs. NON WATER-SOLUBLE

Unless the SOILS and the PLANTS grown in those soils have the 40 plus minerals our bodies need, you need to find a source of supplementation that provides "water-soluble" minerals to ensure you are receiving optimal intake. "Water-soluble" minerals are those that are derived from the vegetables, fruit and grain we eat. These minerals, if supplemented, should be water-soluble also.

The advantage of using water-soluble minerals vs. non water-soluble minerals is that they are essentially non-toxic and are more easily absorbed and used by the body. Also, water-soluble minerals are easily excreted through the urine if your body does not need them.

Mechanism of Action of the Essential- Ultratrace Elements

The essential ultratrace elements are universally required for survival. They normally occur and function in cells at extremely low concentrations, usually far less than one micromolar and as low as IV M. **Our understanding of the biological events that link an ultratrace element to its specific vital function(s) is still fragmentary.** Obviously, the amplification machinery of the organism's enzymes, carrier proteins, hormones, key structural sites-is involved. No single pattern will encompass what is known to date about these metal ions. The dominant theme has been that trace elements are essential because they serve as required coenzymes for irreplaceable metal-ion-activated enzymes or metalloenzymes. **It has been estimated that one-fourth to one-third of all known enzymes involves a metal ion as a required participant.**

In the metalloenzymes, a fixed number of specific metal atoms (usually Fe, Zn, Cu, Mn, Mo, Co, Se, Ni, etc.) are firmly associated with a specific protein. This combination produces a unique enzyme with a unique catalytic function. There are a number of variations on this theme. The metalloenzyme, superoxide dismutase, is isolated from mammalian cytoplasm with two atoms of copper and zinc per molecule. To retain catalytic activity, the zinc ion can be replaced by almost any transition metal ion, but no active replacement for copper is possible. Vallee (1980) has described how cobalt and

various other metal ions can substitute for native zinc atoms in several zinc enzymes (e.g., carboxypeptidase, alkaline phosphatase) with retention of enzyme activity.

Cobalt functions in a complicated system that is not yet understood. Cobalt is an essential component of vitamin B12, the coenzyme for methyl transferase that is necessary for thymidine synthesis and, ultimately, DNA biosynthesis and the transcription process itself. Evolution of iron enzymes and vital iron proteins has taken several major paths, one of which involves porphyrin groups and one of which involves constituent amino acids (cysteine, histidine, tyrosine) of specific proteins. At one time the effects of selenium deficiency were thought to be due primarily to an absence of adequate amounts of glutathione peroxidase leading to excessive hemolysis. More recently, interconversions of methionine and cysteine have been related to this element (Shamberger, 1983).

The two essential nonmetals, iodine and fluorine, have different histories. Iodine is needed for the biosynthesis of thyroid hormones, which in turn greatly affect development and metabolism in all vertebrates. The primary role of fluoride may be in the structural integrity of mineralized tissues. Fluoride's anticaries effect is not regarded as implying the existence of a fundamental fluoride deficiency disease.

As the elements become more ultratrace, establishing deficiency syndromes and identifying their possible coenzymic functions become increasingly difficult. One important advantage is that the metal ion provides a natural label of that part of the protein that is directly involved in the reaction, the active site of the enzyme. The unique spectroscopic properties of metalloenzymes have also been especially valuable in describing events at the active site. The availability and use of a convenient radioactive isotope of the metal becomes almost mandatory. Refinement of atomic absorption analytical instrumentation is another asset in addressing this problem. Certainly the elucidation of the mode of action of the essential ultratrace elements will be a major challenge for future research in biochemistry.

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Nutritional implications of the interactions between minerals.

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It is well recognized that the absorption, retention and metabolism of most essential minerals can be markedly influenced by the presence of antinutrient factors in the diet (i.e. fiber and phytate). However, in addition, interactions can also occur between essential minerals. Indeed, under some circumstances, these interactions can be profound and have significant implications for human health. Interactions between essential minerals can be broadly classified as direct or indirect. Direct interactions are generally competitive phenomena that occur during the intestinal absorption and/or during the tissue utilization of a mineral. Indirect interactions occur when one of the minerals is involved in the metabolism of the other mineral, or when a deficiency or toxicity of one of the minerals results in hormonal changes or tissue damage which affects the metabolism of the other mineral.

NOTE: As explained in other sections of this web site, if the minerals presented to animals or to humans are WATER SOLUBLE, you do not have to worry about interference of the absorption process by substances in the plants (phytates) or about interference of one mineral interacting with another. If the body does not need the mineral or if there is too much of a particular mineral, the body simply excretes what it does not need. Pretty simple.

NOTE: Occasionally you will see the term METALLOTHIONEIN. Below are two explanations/definitions of what this substance is and its relationship with the absorption of minerals.

Prog Food Nutr Sci 1987;11(1):1-37

Interactions between metallothionein and trace elements.

Bremner I

Metallothionein is an important metal-binding protein, which occurs in varying amounts in a wide range of tissues but particularly in liver, kidneys, intestine and pancreas. Synthesis of the protein is induced by zinc and copper and also by cadmium and many other non-essential elements. The concentration of the protein in tissues depend on zinc and copper status and on patho-physiological state. A variety of stress factors stimulate metallothionein synthesis, particularly in liver. The turnover rate of metallothionein in tissues is relatively high but depends to a large extent on its metal content. There has been much speculation as to the function of the protein and one important role appears to lie in the cellular detoxification of copper, zinc and other metals. Metallothionein also appears to participate in metabolic interactions between zinc and copper. The protein occurs in small amounts in blood and urine and assay of these concentrations may be used in the assessment of trace element status.

EXS 1987;52:81-107

Nutritional and physiological significance of metallothionein

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The biological function of metallothionein (MT) is still a matter of considerable conjecture. Convincing evidence has accrued that the protein can play an important role in the detoxification of certain heavy metals (Cd) but a more fundamental role may be concerned with the metabolism of the essential elements zinc and copper. In addition the effects of physical and inflammatory stress and of infection on MT production imply an involvement in defense mechanisms against these conditions. MT may also act as a general detoxifying agent against certain xenobiotics.

Example of reference material with regard to trace elements and a specific medical condition.

Trace Elements in Rheumatoid Arthritis

Rheumatoid arthritis is characterized by increased activity of macrophages, which in cooperation with other inflammatory cells infiltrates the synovial tissue. The activated macrophages generate reactive forms of oxygen, which have been suggested as mediators of inflammation. Gold is accumulated in the lysosomes of the macrophages, which are thereby immobilized, causing an arrest of the proinflammatory signalation. Zinc in high doses can also immobilize macrophages. Gold and zinc as well as copper can induce synthesis of the sulphhydryl-rich protein metallothionein. Copper is a component of the cytosolic enzyme superoxide dismutase, and several copper-containing molecules including ceruloplasmin possess superoxide-dismutating activity.

The anti-inflammatory activity of Cu-complexes is attributed to their SOD activity. The therapeutic effect of penicillamine, as well, may be related to an antioxidative or membrane-protecting action. Increased intracellular levels of GSH and the selenium-containing enzyme GSH-Px can also accelerate the breakdown of reactive oxygen. Future research is of interest to evaluate the therapeutic effect of selenium supplementation.

Below is an example of the essentiality of some newer-researched trace minerals:

FASEB J 1991 Sep;5(12):2661-2667

Nutritional requirements for boron, silicon, vanadium, nickel, and arsenic: current knowledge and speculation.

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Definition of specific biochemical functions in higher animals (including humans) for the ultratrace elements boron, silicon, vanadium, nickel, and arsenic still has not been achieved although all of these elements have been described as being essential nutrients. Recently, many new findings from studies using molecular biology techniques, sophisticated equipment, unusual organisms, and newly defined enzymes have revealed possible sites of essential action for these five elements. Based on these findings and the response of animals and/or humans to low intakes of these elements, the following speculations have been presented: 1) Boron has a role that affects cell membrane characteristics and transmembrane signaling. 2) Silicon is necessary for the association between cells and one or more macromolecules such as osteonectin, which affects cartilage composition and ultimately cartilage calcification. 3) Vanadium reacts with hydrogen peroxide to form a pervanadate that is required to catalyze the oxidation of halide ions and/or stimulate the phosphorylation of receptor proteins. 4) Nickel is needed for the CO₂-fixation to propionyl-CoA to form D-methylmalonyl-CoA. 5) Arsenic has an important role in the conversion of methionine to its metabolites taurine, labile methyl, and the polyamines. If any of these speculations are found to be true, the element involved will be firmly established as having a nutritional requirement because the body obviously cannot synthesize it. Based on animal findings, the dietary requirement is likely to be small; that is, expressed in micrograms per day.