Trace Mineral Deficiencies

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Introduction

By 1940 the concept of essential nutrients was well established; they were defined as chemical substances found in food that could not be synthesized by the body to perform functions necessary for life. In the 1960s and 1970s, the standard for essentiality was liberalized for mineral elements that could not be fed at dietary concentrations low enough to cause death or interrupt the life cycle (interfere with growth, development, or maturation such that procreation is prevented). Thus, an essential element during this time period was defined as one whose dietary deficiency consistently and adversely changed a biological function from optimal, and this change was preventable or reversible by physiological amounts of the element. This definition of essentiality became less acceptable when a large number of elements was suggested to be essential based on small changes in physiological or biochemical variables. Many of these changes were questioned as to whether they were necessarily the result of a suboptimal function, and sometimes were suggested to be the consequence of a pharmacologic or toxic action in the body, including an effect on intestinal microorganisms. As a result, if the lack of an element cannot be shown to cause death or to interrupt the life cycle, many scientists, perhaps a majority, now do not consider an element essential unless it has a defined biochemical function. However, there are still scientists who base essentiality on older criteria. Thus, no universally accepted list of essential trace elements exists. Nonetheless, it is hoped that most of the mineral elements that are essential, possibly essential, or beneficial have been included in this section.

Biological Roles of Mineral Elements

Trace elements have at least five roles in living organisms. In close association with enzymes, some trace elements are integral parts of catalytic centers at which the reactions necessary for life occur. Working in concert with a protein, and frequently with other
organic coenzymes, trace elements are involved in attracting substrate molecules and converting them to specific end products. Some trace elements donate or accept electrons in reactions of reduction or oxidation. In addition to the generation and utilization of metabolic energy, redox reactions frequently involve the chemical transformation of molecules. One trace element, iron, is involved in binding, transporting, and releasing oxygen in the body. Some trace elements have structural roles; that is, imparting stability and three-dimensional structure to important biological molecules. Some trace elements have regulatory roles. They control important biological processes through such actions as inhibiting enzymatic reactions, 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 a cell, and inducing genes to express themselves resulting in the formation of proteins involved in life processes.

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**Homeostatic Regulation of Mineral Elements**

Homeostasis is a term used to describe the ability of the body to maintain the content of a specific substance within a certain range despite varying intakes. Homeostasis involves the processes of absorption, storage, and excretion. The relative importance of these three processes varies among the trace elements. The amount absorbed from the gastrointestinal tract often is a primary controlling factor for trace elements needed in the cationic state such as copper, iron, and zinc. Trace elements absorbed as negatively charged anions, such as boron and selenium, are usually absorbed freely and completely from the gastrointestinal tract. Excretion through the urine, bile, sweat, and breath is, therefore, the primary mechanism for controlling the amount of these trace elements in an organism. By being stored in inactive sites, some trace elements are prevented from causing adverse reactions when present in high quantities. An example of this homeostatic process is the storage of iron in the form of ferritin. Release of a trace element from a storage site also can be important in preventing deficiency.

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**Factors Affecting the Manifestation of Deficiency Signs**

Although trace elements play key roles in a variety of processes necessary for life, except for iodine and iron, the occurrence of overt, simple, or uncomplicated deficiency of any trace element in humans is not common. The reasons for this are the powerful homeostatic mechanisms for trace elements described above, and the consumption of diets with different types of foods from different sources. However, reductions in health and wellbeing because of suboptimal status in some trace elements probably are not uncommon because of other factors affecting their metabolism or utilization. For example, genetic errors and diseases that affect absorption, retention, or excretion of a trace element can result in deficiency pathology even though intake may meet dietary guidelines. In other words, most important in making trace elements of nutritional concern is that their metabolism or utilization can be impaired or their need can be increased by nutritional, metabolic, hormonal, or physiological stressors. This is exemplified by selenium, for which it is difficult to produce signs of pathology caused by a simple deficiency in animals or humans.
Trace Mineral Deficiencies

A stressor such as vitamin E deficiency or viral infection is needed to obtain marked pathology such as that seen with Keshan disease, a cardiomyopathy that primarily affects children and women of childbearing age in some areas of China.

Treatment of Trace Mineral Deficiencies

Because most mineral elements can have adverse effects if taken orally in excess of the Recommended Dietary Allowance (RDA), Estimated Safe and Adequate Daily Dietary Intake (ESADDI), or Adequate Intake (AI), deficiencies of mineral elements are best treated by giving supplements that supply one or two times these amounts. Higher amounts may be indicated if a deficiency is caused by a factor resulting in malabsorption or excessive excretion; these amounts need to be adjusted until indicators of deficiency have been abated and normal status is maintained. The response to treatment of a trace mineral deficiency is best monitored by determining that desirable changes are occurring in indicators of deficiency or status. Once indicators are within normal ranges, intakes near the RDA, ESADDI, or AI that maintain these normal values should be maintained. A diet providing the needed intakes is preferable over supplements.

Mineral Elements Essential for Humans

Essential Trace Elements

Trace elements essential for life generally occur in the body in microgram per gram of tissue, and are usually required by humans in amounts of milligrams per day; these elements are copper, iron, manganese, and zinc. The evidence for essentiality for humans is substantial and noncontroversial for these elements. Specific biochemical functions have been defined for all of them. Another element, boron, has recently joined the list of those accepted as essential; it has been found to be required to complete the life cycle of fish and frogs. Because magnesium has many characteristics of a trace element, it also will be included in this grouping.

Boron

Knowledge about the role and clinical aspects of boron in nutrition is just emerging. The biological function of boron has not been defined, but boron apparently has a role that influences the metabolism and utilization of several other nutrients. Thus, described deficiency signs and the pathological consequences of inadequate boron intake, because they can be affected by the intake of several other dietary substances, are numerous and variable. As a result, providing sound factual descriptions in each of the categories in Table 71.1 is not possible, and the information provided could be changed quickly by new research findings. Indicators of boron status are still being established. However, a plasma boron concentration below 25 ng/mL might be indicative of a low boron status. Changes in biochemical indices affected by physiological amounts of boron (shown in Table 71.1) with boron supplementation also may be an indicator of a low boron status. Most of the information in Table 71.1 can be found in reviews by Nielsen, Hunt, and Penland.
TABLE 71.1
Biochemical, Clinical, and Nutritional Aspects of Boron

**Biological Function:**

Established — None
Hypothesized — 1. A role in cell membrane function that influences the response to hormone action, transmembrane signaling, or transmembrane movement of regulatory cations or anions.
2. A metabolic regulator through complexing with a variety of substrate or reactant compounds in which there are hydroxyl groups in favorable positions. Regulation is mainly negative.

**Signs of Deficiency:**

Biochemical — Because boron apparently affects calcium metabolism and hormone action, low dietary boron has a variety of effects in humans. These include:
- Calcium indicators — Decreased serum 25-hydroxycholecalciferol; increased serum calcitonin
- Energy metabolism — Increased serum glucose; decreased serum triglycerides
- Nitrogen metabolism — Increased blood urea; increased serum creatinine; decreased urinary hydroxyproline excretion
- Reactive oxygen metabolism — Decreased erythrocyte superoxide dismutase; decreased ceruloplasmin
- Response to estrogen — Decreased serum 17β-estradiol; decreased plasma copper

Physiological — Because boron can cause a variety of biochemical responses depending upon other dietary factors, it is not surprising that boron deprivation also has a variety of physiological effects. These include:
- Altered electroencephalograms such that they suggest impaired behavior activation (e.g., more drowsiness) and mental alertness
- Impaired psychomotor skills
- Impaired cognitive processes of attention and memory
- Increased platelet and erythrocyte numbers; decreased white blood cells

A number of physiological signs of deficiency have been found in animals that may eventually have some counterparts in humans. Reported signs 1, 3, 9 include:

- Frog — Increased necrotic eggs; high frequency of abnormal gastrulation in embryo; abnormal development of the gut, craniofacial region, and eye, visceral edema, and kinking of the tail during organogenesis; delayed tail absorption during metamorphosis
- Zebrafish — Embryo death during the zygote and cleavage periods before the formation of a blastula during embryo development; photophobia characterized by photoreceptor dystrophy in adults
- Rat — Exacerbation of distortion of marrow sprouts and delay in the initiation of cartilage calcification in bones during marginal vitamin D deficiency; decreased circulating concentrations of natural killer cells and CD8a+CD4+ cells during antigen-induced arthritis

**Pathological Consequences of Deficiency:**

Established — None
Hypothesized — Increased susceptibility to osteoporosis and arthritis
  - Impaired cognitive and psychomotor function

Predisposing factors for deficiency: stressors affecting calcium metabolism and utilization especially low dietary intakes of vitamin D or calcium; stressors affecting cell membrane function or signal transduction including low dietary intakes of magnesium, potassium or copper

**Recommended Intakes:**

Prevention of deficiency — Suggested to be 1.0 mg/day
Therapeutic or beneficial — Luxuriant intakes (e.g., 3 mg/day) may be beneficial when stressors are present that lead to osteoporotic or arthritic changes

**Food Sources:**

Food and drink of plant origin, especially noncitrus fruits, leafy vegetables, nuts, pulses, legumes, wine, cider
Copper

Although copper is a well-established essential trace element, its practical nutritional importance, and thus its dietary requirement, remain debatable. Well-established consequences of copper deprivation in humans have come mainly from findings with premature infants and infants with the genetic disorder Menkes’ disease; other consequences have been projected from epidemiological, animal, and short-term human copper depletion findings. Most of the information found in Table 71.2 has been obtained from reviews by Harris,10 Klevay and Medeiros,11 Milne,12 Cordano,13 and Uauy et al.14

Iron

Among the mineral nutrients, iron has the longest and best described history. Despite long and effective intervention activities, iron deficiency is the primary mineral deficiency in the U.S. and the world. Recently, it has been suggested that high intakes of iron also may be a health concern. Table 71.3 only briefly outlines some important aspects of iron nutrition, using information from reviews by Beard and Dawson28 and Baynes and Stipanuk.29

Magnesium

Magnesium is the fourth most abundant cation in the body and is second only to potassium in its intracellular concentration. This concentration reflects that magnesium is critical for a great number of cellular functions including oxidative phosphorylation, glycolysis, DNA transcription, fatty acid degradation, and protein synthesis. Surprisingly, although it is such a critically important element, reported descriptions of signs and symptoms of magnesium deficiency in humans through dietary restriction alone are very limited. Described cases of clinical magnesium deficiency have generally been conditioned deficiencies where factors interfering with absorption or promoting excretion were present (see Table 71.4). Table 71.4 briefly outlines some of the important aspects of magnesium nutrition using information from reviews by Rude40 and Shils.41

Manganese

The essentiality of manganese for animals has been known for over 50 years. Deficiency causes testicular degeneration (rats), slipped tendons (chicks), osteodystrophy, severe glucose intolerance (guinea pigs), ataxia (mice, mink), depigmentation of hair, and seizures. However, only one description of an unequivocal case of human manganese deficiency has been reported. A child with a postoperative short bowel receiving over 90% of her nutrition parenterally, which was low in manganese, developed short stature and brittle bones. Because manganese deficiency has been so difficult to identify in humans, manganese is considered not of nutritional concern. Most of the information in Table 71.5 has been obtained from reviews by Leach and Harris,49 Nielsen,50 and Freeland-Graves and Llanes.51

Zinc

Signs of zinc deficiency in humans were first described in the 1960s. However, the prevalence of zinc deficiency is controversial because of the lack of satisfactory indicators of zinc status. Nonetheless, unquestionable zinc deficiency has been induced often by providing zinc-deficient total parenteral nutrition (TPN), and by feeding cow’s milk to infants who have a genetic inability to absorb zinc from such a source. The information in Table 71.6 primarily comes from reviews by Chesters,60 Prasad,61 and Sandstead.62
TABLE 71.2
Biochemical, Clinical, and Nutritional Aspects of Copper

**Biological Function:**

Copper is a cofactor for a number of oxidase enzymes and has roles in angiogenesis, neurohormone release, oxygen transport, and the regulation of genetic expression. Copper enzymes are involved in the generation of oxidative energy, oxidation of ferrous iron, synthesis of neurotransmitters, bestowment of pigment to hair and skin, provision of strength to bones and arteries, assurance of competence of the immune system, and stabilization of the matrices of connective tissues. These enzymes include: lysyl oxidase, ferrooxidase (ceruloplasmin), dopamine B-monoxygenase, tyrosinase, alpha-amidating monoxygenase, cytochrome c oxidase, and superoxide dismutase.

**Signs of Deficiency:**

Biochemical — Although not consistently seen, the following have been reported to be the result of copper deprivation in humans: decreased erythrocyte superoxide dismutase; decreased enzymatic and immunoreactive ceruloplasmin and ratio; decreased platelet and mononuclear white cell cytochrome c oxidase; increased plasma LDL and total cholesterol; increased plasma glutathione; decreased platelet and plasma copper; decreased plasma HDL cholesterol and interleukin-2.

Physiological — Premature and malnourished infants: hematologic changes characterized by hypochromic, normocytic or macrocytic anemia accompanied by reduced reticulocyte count, neutropenia and thrombocytopenia; bone abnormalities which mimic scurvy by showing osteoporosis, fractures of the long bones and ribs, epiphyseal separation, fraying and cupping of the metaphyses with spur formation, and subperiostal new bone formation; hypopigmentation of hair; impaired growth; impaired immunity. Adults (reported experimentally induced): abnormal electrocardiograms; impaired glucose tolerance; increased blood pressure with exercise.

**Pathological Consequences of Deficiency:**

Established — Premature and malnourished infants: anemia; osteoporosis and bone fractures; increased incidence of infections; poor growth; Menkes' disease; “kinky-type” steely hair; progressive neurologic disorder; death.

Hypothesized — Fetus and children: impaired brain development; 15,16 teratogenesis. 17, 18 Adults: osteoporosis, ischemic heart disease, 20-22 increased susceptibility to infections, 23 and cancer, 25 accelerated aging. 26

**Predisposing Factors for Deficiency:**

Factors causing impaired absorption including high intakes of iron and zinc, celiac disease, short bowel syndrome, cystic fibrosis, tropical and nontropical sprue, diarrhea, and jejunoileal bypass surgery; and factors causing excessive copper loss including ambulatory peritoneal dialysis, burn trauma, penicillamine therapy, dexamethasone treatment, and excessive use of antacids.

**Recommended Intakes:**

Prevention of deficiency — The estimated safe and adequate daily dietary intakes (in mg/day) are: infants age 0-0.5 years, 0.4-0.6 and age 0.5-1 year, 0.6-0.7; children and adolescents age 1-3 years, 0.7-1.0, age 4-6, 1.0 1.5, age 7-10 years, 1.0-2.0, and age 11+ years, 1.5-2.5; adults, 1.5-3.0. 27 The lack of a recommended dietary allowance for copper indicates that the amount needed to prevent deficiency is a debatable issue. Therapeutic or beneficial — Increased intakes of copper (e.g., 3 mg/day) may be beneficial in preventing osteoporosis, overcoming the adverse effects of high zinc intake, and more quickly overcoming the consequences of copper deficiency.

**Food Sources:**

Legumes, whole grains, nuts, organ meats (e.g., liver), seafood (e.g., oysters, crab), peanut butter, chocolate, mushrooms, ready-to-eat cereals.
TABLE 71.3
Biochemical, Clinical, and Nutritional Aspects of Iron

**Biological Function:**
Iron is involved in oxygen transport and storage, electron transport, and in numerous enzymatic reactions involving substrate oxidation and reduction. The classes of enzymes dependent on iron for activity include the oxidoreductases exemplified by xanthine oxidase/dehydrogenase, monoxygenases exemplified by the amino acid oxidases and cytochrome P450, dioxygenases exemplified by amino acid or amine dioxygenases, lipooxygenases, peroxidases, fatty acid desaturases and NO synthases, and miscellaneous enzymes such as aconitase.

**Signs of Deficiency:**
Biochemical — Decreased tissue and blood iron enzymes, myoglobin, hemoglobin, ferritin, transferrin saturation, and iron; increased erythrocyte protoporphyrin
Physiological — Anemia, glossitis, angular stomatitis, spoon nails (koilonychia), blue sclera, lethargy, apathy, listlessness, and fatigue

**Pathological Consequences of Deficiency:**
Established — Impaired thermoregulation, immune function, mental function, and physical performance; complications in pregnancy including increased risk of premature delivery, low birth weight, and infant morbidity
Hypothesized — Osteoporosis, abnormal brain development

**Predisposing Factors for Deficiency:**
Blood loss including that through menstruation; vegetarian diets

**Recommended Intakes:**
Prevention of deficiency — The recommended dietary allowances (RDA) for iron (in mg/day) are: infants age 0-0.5 years, 6; and age 0.5-1 year, 10; children 1-10 years, 10; males age 11-18 years, 12; age 19+ years, 10; females age 11-50, 15; and age 50+, 10; pregnant females, 30; lactating females, 15. Therapeutic or beneficial — Higher doses than the above can be given to more quickly overcome iron deficiency, usually caused by blood loss; doses used include 50-60 mg/day or 120 mg/week. However, caution is in order because high intakes of iron have been associated with cardiovascular disease, cancer, and neurodegenerative disorders.

**Food Sources:**
Red meat, organ meats (e.g., liver), seafood (e.g., oysters, shrimp), fortified cereals, potatoes with skin, tofu; some whole grains and vegetables (e.g., spinach) are high in iron, but the bioavailability of this iron may be low
TABLE 71.4
Biochemical, Clinical, and Nutritional Aspects of Magnesium

**Biological Function:**

Magnesium is a cofactor for more than 300 enzymes in the body. This cofactor role is either as a direct allosteric activator of enzymes or as a part of enzyme substrates for some enzyme reactions (e.g., MgATP and MgGTP). Magnesium also has functions that affect membrane properties and thus influence potassium and calcium channels and nerve conduction.

**Signs of Deficiency:**

Biochemical — Low blood potassium, calcium, and magnesium; decreased intracellular potassium; excessive renal potassium excretion; impaired parathyroid hormone excretion and vitamin D function; renal and skeletal resistance to parathyroid hormone

Physiological — Neuromuscular signs (e.g., positive Trousseau's sign, tremors, fasciculations, gross muscle spasms, muscle cramps and weakness, seizures, dizziness, disequilibrium); electrocardiographic abnormalities; cardiac arrhythmias (e.g., rapid heart rate, ventricular premature discharges, atrial and ventricular fibrillation)

**Pathological Consequences of Deficiency:**

Established — Conditioned deficiencies result in cardiac disorders, seizures, cramps, depression, and psychosis

Hypothesized — Numerous epidemiological findings and magnesium supplementation trials show that low magnesium status is associated with numerous disorders including coronary heart disease, hypertension, migraine headaches, sleep disorders, mood disturbances, and osteoporosis

**Predisposing Factors for Deficiency:**

Factors interfering with absorption or promoting excretion including alcoholism, cirrhosis, kidney failure, malabsorption syndromes, extensive bowel resection, gastroileal bypass, severe or prolonged diarrhea, protein-calorie malnutrition, acute pancreatitis, hyperaldosteronism, diabetes mellitus, thyroid gland disease, parathyroid gland disease, vitamin D-resistant rickets, pellagra, malignant osteolytic disease, burns and diuretic therapy

**Recommended Intakes:**

Prevention of deficiency — The recommended dietary allowances (RDA) for magnesium (in mg/day) are: children age 1-3 years, 80; age 4-8 years, 130; and age 9-13 years, 240; male adults age 14-18 years, 410, age 19-30 years, 400, and age 31+ years, 420; female adults age 14-18 years, 360, age 19-30 years, 310, and age 31+ years, 320; pregnant females, +40. Adequate intakes have been indicated for infants; they are for age 0.5 years, 30, and age 0.5-1 years, 75.

Therapeutic or beneficial — Although the infusion of magnesium has been suggested as a therapeutic measure to reduce the frequency of arrhythmias and mortality in cases of suspected acute myocardial infarction, this has not been confirmed in large trials.

**Food Sources:**

Whole grains, nuts, legumes, green leafy vegetables
### TABLE 71.5

Biochemical, Clinical, and Nutritional Aspects of Manganese

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**Biological Function:**

Manganese is a cofactor for enzymes involved in protein and energy metabolism, antioxidant action, and mucopolysaccharide synthesis. These enzymes include the metalloenzymes manganese-dependent superoxide dismutase, pyruvate carboxylase and arginase, and the manganese-activated enzymes phosphoenolpyruvate carboxykinase, glycosyl transferases, glutamine synthetase, and farnesyl pyrophosphate synthetase.

**Signs of Deficiency:**

Biochemical — Possible signs include hypocholesterolemia, and increased serum calcium, phosphorus and alkaline phosphatase activity.

Physiological — Impaired growth and brittle bones; another possible sign is a fleeting dermatitis

**Pathological Consequences of Deficiency:**

Established — Osteoporosis (one case report in a child)\(^5^2\)

Hypothetical — Low dietary manganese or low blood and tissue manganese has been associated with osteoporosis,\(^5^3\) epilepsy,\(^5^4\) atherosclerosis,\(^5^5\) impaired wound healing,\(^5^6\) and increased susceptibility to cancer\(^5^7,5^8\)

Predisposing factors for deficiency: High dietary intakes of calcium, phosphorus, iron, fiber, phytates and polyphenolic compounds

**Recommended Intakes:**

Prevention of deficiency — The estimated safe and adequate daily dietary intakes for manganese (in mg/day) are: infants age 0-0.5 years, 0.3-0.6, and age 0.5-1 year, 0.6-1.0; children and adolescents age 1-3 years, 1.0-1.5, age 4-6 years, 1.5-2.0, age 7-10 years, 2.0-3.0, and age 11+ years, 2.0-5.0; adults, 2.0-5.0.\(^2^7\)

Therapeutic or beneficial — High intakes of manganese are ill-advised because of potential neurotoxicological effects,\(^5^9\) especially in people with compromised homeostatic mechanisms, or infants whose homeostatic control of manganese is not fully developed.

**Food Sources**

Unrefined grains, nuts, green leafy vegetables, and tea
TABLE 71.6
Biochemical, Clinical, and Nutritional Aspects of Zinc

**Biological Function:**

Zinc is unique in that it is the only trace element with essential actions in all six enzyme classes. Over 50 zinc metalloenzymes have been identified. Another function of zinc is as a component of transcription factors also known as zinc finger proteins that bind to DNA and activate transcription of a message. Zinc also imparts stability to cell membranes.

**Signs of Deficiency:**

- Biochemical — Decreased plasma and leukocyte zinc, plasma metallothionein, thymulin and alkaline phosphatase, and extracellular superoxide dismutase; increased plasma 5’-nucleotidase and platelet amyloid precursor protein

- Physiological — Depressed growth; anorexia; parakeratotic skin lesions; diarrhea; impaired testicular development, immune function, and cognitive function

**Pathological Consequences of Deficiency:**

- Established — Dwarfism, delayed puberty, failure to thrive (acrodynatititis enteropathica infants), impaired wound healing, and increased susceptibility to infectious disease

- Hypothesized — Osteoporosis, infertility, teratogenesis, increased susceptibility to diabetes, and rheumatic disease, especially rheumatoid arthritis

**Predisposing Factors for Deficiency:**

Factors affecting absorption including phytate intake, vegetarianism, intestinal infestation by bacteria, protozoa and helminths, gastric and intestinal resection, inflammatory bowel disease, exocrine pancreatic insufficiency, biliary obstruction, and high intakes of copper and iron; factors increasing loss including protein losing enteropathies, renal failure, renal dialysis, diuretic therapy; chronic blood loss (e.g., sickle cell disease), exfoliative dermatoses; factors increasing utilization including rapid tissue synthesis and postcatabolic convalescence.

**Recommended Intakes:**

- Prevention of deficiency — The recommended dietary allowances (RDA) for zinc (in mg/day) are: infants age 0-1.0 year, 5; children age 1-10 years, 10; males age 11-51+ years, 15; females age 11-51+ years, 12; pregnant females, 15; lactating females, first 6 months, 19, second 6 months, 16.

- Therapeutic or beneficial — High zinc intakes have been used for the alleviation and prevention of colds, treatment of macular degeneration, acute diarrhea and Wilson’s disease; doses have ranged from 20 mg day for children with diarrhea to 150 mg/day for treatment of Wilson’s disease.

**Food Sources:**

Red meats, organ meats (e.g., liver), shellfish, nuts, legumes
Essential Ultra Trace Elements

In 1980, the term ultra trace elements began to appear in the nutritional literature; the definition for this term was an element required by animals in amounts of 50 nanograms or less per gram of diet. For humans, the term has been used recently to indicate elements with established or estimated requirements quantified by micrograms per day. Five elements fit in this category. The evidence of essentiality for humans is substantial and noncontroversial for cobalt, iodine, molybdenum, and selenium; specific biochemical functions have been identified for all of them. Another element, chromium, has recently joined the list of ultra trace elements accepted as essential because a defined biochemical function has been identified for it.

Chromium

Many nutritionists have considered chromium as essential for humans since 1977, when a subject on long-term TPN apparently containing a low amount of chromium developed impaired glucose tolerance and insulin resistance that were reversed by an infusion of chromium. However, not until 1997 did evidence come forth which conclusively showed that chromium was essential; then a biochemical function was identified for chromium. Nonetheless, since 1966 numerous reports have described beneficial effects from chromium supplements in subjects with degrees of glucose intolerance ranging from hypoglycemia to insulin-dependent diabetes. The information in Table 71.7 comes primarily from reviews by Anderson, Nielsen, and Lukaski.

Cobalt

Ionic cobalt is not an essential nutrient for humans; however, vitamin B₁₂, in which cobalt is an integral component, is an essential nutrient for humans. In the 19th century, a megaloblastic anemia was described that was called pernicious anemia because it was invariably fatal. The first effective treatment for this disease was one pound of raw liver daily. In 1948, the anti-pernicious anemia factor in liver was isolated and named vitamin B₁₂, and was found to contain 4% cobalt. Vitamin B₁₂ deficiency is rarely caused by a dietary insufficiency and most commonly arises from a defect in vitamin B₁₂ absorption. People with low vitamin B₁₂ status (e.g., vegetarians) can also display signs of deficiency if stressed with a substance such as nitrous oxide (used in dentistry), which inhibits vitamin B₁₂ activity. Most of the information in Table 71.8 was obtained from reviews by Herbert, Smith, Shane, and Nilsson-Ehle.

Iodine

The consequences of iodine deficiency, which is common, are so profound that it is one of the largest public health problems in the world today. Recognition that iodine was nutritionally important began in the 1920s when it was found that iodine prevented goiter, and increased iodine intake was associated with decreased endemic cretinism. Most of the information in Table 71.9 has been obtained from reviews by Freake and Hetzel and Wellby.

Molybdenum

Because molybdenum is a cofactor for some enzymes, its essentiality is well established. However, molybdenum deficiency has not been unequivocally identified in humans other than in an individual nourished by TPN and in individuals with a genetic disease that
TABLE 71.7
Biochemical, Clinical, and Nutritional Aspects of Chromium

**Biological Function:**

A naturally occurring biologically active form of chromium named Low-Molecular-Weight Chromium-Binding Substance (LMWCr) has been identified that has a role in carbohydrate and lipid metabolism as part of a novel insulin-amplification mechanism. LMWCr is an oligopeptide of about 1500 Da that binds four chromic ions and potentiates the ability of insulin to stimulate the conversion of glucose into lipids and carbon dioxide by isolated rat adipocytes.

**Signs of Deficiency:**

- Elevated serum glucose, cholesterol, triglycerides and insulin; glycosuria; decreased insulin binding and insulin receptor number
- Impaired glucose tolerance

**Pathological Consequences of Deficiency:**

- Impaired glucose tolerance
- Diabetes, atherosclerosis, impaired immune function, increased susceptibility to osteoporosis

**Predisposing Factors for Deficiency:**

Factors promoting urinary excretion including acute exercise, physical trauma, lactation, and high dietary simple sugars; and factors inhibiting absorption including phytate and drugs that reduce stomach acidity (e.g., antacids) or alter gastrointestinal prostaglandins (e.g., dimethylprostaglandin)

**Recommended Intakes:**

Prevention of deficiency — The estimated safe and adequate daily dietary intakes for chromium (in μg/day) are: infants age 0 to 0.5 years, 10-40; and age 0.5-1 year, 20-60; children and adolescents age 1-3 years, 20-80, age 4-6 years, 30-120, and age 7 years and older, 50-200; adults, 50-200. 27 Therapeutic or beneficial — Doses of 200-1000 μg/day of chromium have been shown to potentiate the action of low amounts of insulin or improve the efficacy of insulin such that the need for exogenous sources is reduced or eliminated for some type II diabetics.

**Food Sources:**

Whole grains, pulses (e.g., dried beans), some vegetables (including broccoli and mushrooms), liver, processed meats, ready-to-eat cereals, spices
TABLE 71.8
Biochemical, Clinical, and Nutritional Aspects of Cobalt

Biological Function:

Vitamin B₁₂ is a cofactor for two enzymes, methionine synthase which methylates homocysteine to form methionine, and methylmalonyl CoA mutase which converts L-methylmalonyl CoA, formed by the oxidation of odd-chain fatty acids, to succinyl CoA.

Signs of Deficiency:

Biochemical — Decreased erythrocyte and plasma folate, and plasma vitamin B₁₂; increased plasma homocysteine and urinary formiminoglutamate and methylmalonate
Physiological — Megablastic anemia; spinal cord demyelination and peripheral neuropathy

Pathological Consequences of Deficiency:

Established — Pernicious anemia, memory loss, dementia, irreversible neurological disease called subacute degeneration of the spinal cord, death
Hypothesized — Cardiovascular disease associated with elevated plasma homocysteine

Predisposing Factors for Deficiency:

Factors resulting in malabsorption including Type A atrophic gastritis, Helicobacter pylori infection, GI bacteria overgrowth caused by achlorhydria and intestinal blind loops, total gastrectomy leading to loss of intrinsic factor excretion, pancreatic insufficiency and coeliac disease; drugs affecting utilization such as histamine H₂ receptor antagonists and proton pump inhibitors, and oral biguanides used in the treatment of type II diabetes; vegetarian diets; nitrous oxide anesthesia.

Recommended Intakes:

Prevention of deficiency — The recommended dietary allowances (RDA) for vitamin B₁₂ (in µg/day) are: infants age 0-0.5 year, 0.3 and age 0.5-1 year, 0.6; children age 1-3 years, 1.0; age 4-6 years, 1.1; and age 7-10 years, 1.4; males age 11-14 years, 1.7, and age 14 years and older, 2.0; females age 11-14 years, 1.4, age 15-18 years, 1.5, and age 19 years and older, 1.6; pregnant females, 2.2; lactating females 2.1.⁷⁶
Therapeutic or beneficial — Milligram doses are used to treat vitamin B₁₂ malabsorption deficiency syndromes; a common dose is 1 mg/day of oral Vitamin B₁₂ or monthly injections of a minimum of 100 µg of vitamin B₁₂.

Food Sources:

Meat, dairy products, some seafoods, fortified cereals
TABLE 71.9
Biochemical, Clinical, and Nutritional Aspects of Iodine

**Biological Function:**

Iodine has only one function; it is a component of thyroid hormones. However, thyroid hormones have an impact on a wide range of metabolic and developmental functions.

**Signs of Deficiency:**

Biochemical — Decreased plasma or serum thyroxine (T₄) and triiodothyronine (T₃), and urinary iodine; increased plasma or serum thyroid-stimulating hormone (TSH) and cholesterol

Physiological — Decreased basal metabolic rate; decreased heart rate, size, stroke volume, and output; reduced muscle mass and delayed skeletal maturation; abnormal production of glial cells and myelogenesis

**Pathological Consequences of Deficiency:**

Established — The spectrum of iodine deficiency disorders is large and includes fetal congenital anomalies and perinatal mortality; neurological cretinism characterized by mental deficiency, deaf mutism, spastic diplegia, and squint; psychomotor defects; goiter; fatigue, slowing of bodily and mental functions, weight increase and cold intolerance caused by slowing of the metabolic rate

**Predisposing Factors for Deficiency:**

Residence in an area with low soil iodine, lithium treatment, and possibly selenium deprivation

**Recommended Intakes:**

Prevention of deficiency — The recommended dietary allowances (RDA) for iodine (in µg/day) are: infants age 0-0.5 years, 40, and age 0.5-1 year, 50; children age 1-3 years, 70, age 4-6 years, 90, and age 7-10 years, 120; males and females age 11+, 175; pregnant females, 200.²⁷

Therapeutic or beneficial — Iodized oil, in which the fatty acids are chemically modified by iodination, slowly releases iodine over a period of months or years in the body. In populations with a high prevalence of severe iodine deficiency disorders (goiter incidence 30% or more), 1 ml of iodized oil containing 480 mg of iodine administered orally or by injection is a therapeutic measure for long term protection against iodine deficiency. An oral iodide dose of 30 mg monthly, or 8 mg biweekly has been found to be an effective prophylaxis for iodine deficiency.⁸¹

**Food Sources:**

Iodized salt has been the major method for assuring adequate iodine intake since the 1920s. Other sources are seafoods and foods from plants grown on high-iodine soils.

results in a sulfite oxidase (a molybdoenzyme) deficiency. The information in Table 71.10 has been obtained primarily from reviews by Nielsen.⁵⁰,⁷²

**Selenium**

Although selenium was first suggested to be essential in 1957, this was not firmly established until a biochemical role was identified in 1972. The first report of human selenium deficiency appeared in 1979; the subject resided in a low-selenium area and was receiving TPN after surgery. The practical nutritional importance of selenium is still being established, but findings of selenium-responsive disorders in certain populations (e.g., Keshan disease in China), and selenium supplementation resulting in reduced incidence of certain cancers suggest that it is quite important. The information in Table 71.11 primarily comes from reviews by Sunde,⁸⁴,⁸⁵ and Levander and Burk.⁶
Table 71.10
Biochemical, Clinical, and Nutritional Aspects of Molybdenum

**Biological Function:**

In humans, three molybdoenzymes have been identified; these are aldehyde oxidase, xanthine oxidase/dehydrogenase, and sulfite oxidase in which molybdenum exists as a small nonprotein factor containing a pterin nucleus. Molybdoenzymes oxidize and detoxify various pyrimidines, purines, and pteridines; catalyze the transformation of hypoxanthine to xanthine and xanthine to uric acid; and catalyze the conversion of sulfite to sulfate.

**Signs of Deficiency:**

- Biochemical — TPN patient: hypermethioninemia, hypouricemia, hyperoxypurinemia, hypouricosuria, low urinary sulfate excretion
- Genetic sulfite oxidase deficiency patients: increased plasma and urine sulfite, sulfate, thiosulfate, S-sulfocysteine, taurine
- Physiological — TPN patient: mental disturbances progressing to coma. Genetic sulfite oxidase deficiency patients: seizures, brain atrophy/lesions

**Pathological Consequences of Deficiency:**

- Established — Genetic sulfite oxidase deficiency patients: mental retardation, dislocated lenses, death at early age
- Hypothesized — Increased susceptibility to cancer

**Predisposing Factors for Deficiency:**

None known; high sulfur amino acid intake possibly could increase the need for molybdenum

**Recommended Intakes:**

Prevention of deficiency — The estimated safe and adequate daily dietary intakes for molybdenum (in μg/day) are: infants age 0-0.5 years, 15-30; age 0.5-1 year, 20-40; children and adolescents age 1-3 years, 25-50; age 4-6 years, 30-75; age 7-10 years, 50-150; age 11+ years, 75-250; adults, 75-250. Recent findings suggest that an intake of 25 μg/day would be sufficient to prevent deficiency signs.

**Therapeutic or beneficial** — None have been proposed.

**Food Sources:**

Milk and milk products, dried legumes, pulses, organ meats (e.g., liver and kidney), cereals, baked goods
TABLE 71.11
Biochemical, Clinical, and Nutritional Aspects of Selenium

**Biological Function:**

Selenium is a component of enzymes that catalyze redox reactions; these enzymes include various types of glutathione peroxidases and iodothyronine 5'-deiodinases, and thioredoxin reductase.

**Signs of Deficiency:**

*Biochemical* — Decreased plasma and erythrocyte selenium, plasma selenoprotein P and erythrocyte glutathione peroxidase
*Physiological* — Bilateral muscular discomfort, muscle pain and wasting, cardiomyopathy

**Pathological Consequences of Deficiency:**

Established — In the presence of other contributing factors, Keshan disease, a multiple focal myocardial necrosis resulting in acute or chronic heart function insufficiency, heart enlargement, arrhythmia, pulmonary edema, and death; other consequences include mood disturbances\(^87\) impaired immune function, and increased susceptibility to viral infections\(^86\)
Hypothesized — Increased susceptibility to certain types of cancer;\(^89\) Kashin-Beck disease, an endemic osteoarthritis

**Predisposing Factors for Deficiency:**

Conditions that increase oxidative stress including vitamin E deficiency and coxsackievirus B3 infection

**Recommended Intakes:**

Prevention of deficiency — The recommended dietary allowances (RDA) for selenium (in μg/day) are: infants age 0-0.5 years, 10, and age 0.5-1 year, 15; children age 1-6 years, 20, and age 7-10 years, 30; males age 11-14 years, 40, age 15-18 years, 50, and age 19 years and over, 70; females age 11-14 years, 45, age 15-18 years, 50, and age 19 years and over, 75; pregnant females, 65; lactating females, 75.\(^7\)
Therapeutic or beneficial — A supplement of 200 μg/day of selenium was found to have cancer protective effects.\(^80, 81\)

**Food Sources:**

Fish, eggs and meat from animals fed luxuriant selenium, grains grown on high-selenium soil

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**Possibly Essential Ultra Trace Elements**

Circumstantial evidence often is used to contend that an element is essential. This evidence generally fits into four categories. These are:

1. A dietary deprivation in some animal model consistently results in a changed biological function, body structure, or tissue composition that is preventable or reversible by an intake of an apparent physiological amount of the element in question.
2. The element fills the need at physiological concentrations for a known *in vivo* biochemical action to proceed *in vitro*.
3. The element is a component of known biologically important molecules in some life form.
4. The element has an essential function in lower forms of life.
An element is considered to have strong circumstantial support for essentiality if all four types of evidence exist for it. There is strong circumstantial evidence for the essentiality of arsenic, nickel, silicon, and vanadium; thus, they are considered possibly essential ultra trace elements.

Arsenic

In addition to the information in Table 71.12, other findings supporting arsenic essentiality are that arsenic can activate some enzymes in vitro, enhance DNA synthesis in unsensitized

<table>
<thead>
<tr>
<th>Table 71.12</th>
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</thead>
<tbody>
<tr>
<td>Arsenic: Biological Function in Lower Forms of Life, Deficiency Signs in Animals, and Speculated Importance and Postulated Adequate Intake for Humans</td>
</tr>
</tbody>
</table>

**Biological Function in Lower Forms of Life:**

A biochemical function for arsenic has not been identified in lower forms of life, although a bacterium *Chrysozoon arsenatis* reduces $\text{As}^{5+}$ to $\text{As}^{3+}$ to gain energy for growth. However, there are enzymes in higher animals and humans that methylate arsenic with S-adenosylmethionine as the methyl donor. Arsenite methyltransferase methylates arsenite to monomethylarsenic acid, which is methylated by monomethylarsenic acid methyltransferase to yield dimethylarsinic acid, the major form of arsenic in urine.

**Possible Biological Function in Humans:**

Arsenic might have a function that affects the formation and utilization of labile methyl groups arising from methionine. Through this effect on methyl group metabolism, arsenic possibly affects the methylation of important molecules such as DNA.

**Deficiency Signs in Experimental Animals:**

- **Chick** — Depressed growth
- **Goat** — Depressed growth and serum triglycerides; abnormal reproduction characterized by impaired fertility and elevated perinatal mortality; death during lactation with myocardial damage
- **Hamster** — Depressed plasma taurine and hepatic S-adenosylmethionine; elevated hepatic S-adenosylhomocysteine
- **Pig** — Depressed growth; abnormal reproduction characterized by impaired fertility and elevated perinatal mortality
- **Rat** — Depressed growth and hepatic putrescine, spermidine, spermine and S-adenosylmethionine; elevated hepatic S-adenosylhomocysteine; abnormal reproduction

**Speculated Importance for Humans:**

Decreased serum arsenic concentrations in patients undergoing hemodialysis correlated with injuries to the central nervous system, vascular diseases, and cancer

**Predisposing Factors for Deficiency:**

Stressors that affect sulfur amino acid or labile methyl group metabolism including high dietary arginine and selenium, low dietary methionine, zinc, selenium and choline, and taurine and guanidoacetic acid supplementation

**Postulated Adequate Intake for Humans:**

Based on the possible requirements for experimental animals, a possible arsenic requirement of 12 to 25 μg/day has been suggested for humans.

**Food Sources:**

Shellfish, fish, grains, cereal products
human lymphocytes and in those stimulated by phytohemagglutinin, and induce the isolated production of certain proteins known as heat shock or stress proteins. The control of production of these proteins is apparently at the transcriptional level, and may involve changes in methylation of core histones. Arsenic can increase the methylation of the p53 promoter in human lung cells. Interestingly, although arsenic is commonly thought to be carcinogenic, it has recently been found to be effective in the treatment of some forms of leukemia.\textsuperscript{92,93} The information in Table 71.12 primarily comes from reviews by Nielsen.\textsuperscript{50,94,95}

**Nickel**

By 1984, extensive signs of nickel deprivation had been reported for six animal species. Unfortunately, many of the reported signs may have been misinterpretations of pharmacologic actions because nickel was provided in relatively high amounts to supplemented controls in some experiments. Thus, many of the early reported nickel deprivation findings are not shown in Table 71.13. The information in Table 71.13 primarily comes from reviews by Nielsen,\textsuperscript{50,72,95,98} and Eder and Kirchgessner.\textsuperscript{99}

**Silicon**

In addition to the information in Table 71.14, other findings supporting silicon essentiality include its localization in the active growth areas, or osteoid layer, and within the osteoblasts in young bone of mice and rats; its consistent presence in collagen and glycosaminoglycan fractions in several types of connective tissue; and its requirement for maximal bone prolylhydroxylase activity in bone tissue culture. Also, silicon nutriment can affect the response to other dietary manipulations; for example, silicon supplementation can prevent the accumulation of aluminum in the brains of rats fed a diet low in silicon and calcium and high in aluminum. The information in Table 71.14 primarily comes from reviews by Nielsen\textsuperscript{50,94,95,98} and Carlisle.\textsuperscript{100}

**Vanadium**

In addition to the information in Table 71.15, other findings supporting vanadium essentiality have come from in vitro studies with cells and pharmacologic studies with animals. These studies have shown that vanadium has insulin-mimetic properties, stimulates cell proliferation and differentiation, affects cell phosphorylation-dephosphorylation, and affects oxidation-reduction processes. The information in Table 71.15 primarily comes from reviews by Nielsen\textsuperscript{50,72,94,95,98,101,102} and Willsky et al.\textsuperscript{103}

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**Other Elements with Beneficial or Biological Actions**

If an element has only one or two types of circumstantial evidence to support essentiality, it generally does not get widespread support for being a possibly essential element. However, some of these elements have beneficial pharmacological actions (fluoride and lithium), and others may eventually be found to be of some importance from the nutritional point of view. Elements that fit into this category include aluminum, bromine,
TABLE 71.13
Nickel. Biological Function in Lower Forms of Life, Deficiency Signs in Animals, and Speculated Importance and Postulated Adequate Intake for Humans

**Biological Function in Lower Forms of Life:**

Component of urease from bacteria, mycoplasma, fungi, yeast, algae, higher plants, and invertebrates; present in hydrogenases from over 35 species of bacteria, may be a common constituent of hydrogenases that function physiologically to oxidize rather than evolve H₂; component of carbon monoxide; (acceptor) oxidoreductase found in acetogenic, methanogenic, phototrophic, and sulfate-reducing anaerobic bacteria; component of a tetrapyrrole known as factor F₅₃0 found in methyl-S-coenzyme-M reductase that converts CO₂ to methane in methanogenic bacteria; required for the hydrogenase gene to be expressed in *Bradyrhizobium japonicum.*

**Possible Functions in Humans:**

Cofactor in enzymes involved in hydrolysis or redox reactions; stabilization of a biological molecule; regulation of gene expression; regulation of a cellular calcium channel

**Deficiency Signs in Experimental Animals:**

- **Chick** — Depressed hematocrits; ultrastructural abnormalities in the liver
- **Cow** — Depressed ruminal urease activity, serum urea nitrogen, growth
- **Goat** — Depressed growth, hematocrits, reproductive performance
- **Ff** — Depressed growth; altered distribution and proper functioning of zinc and calcium
- **Rat** — Depressed growth, hematocrits, plasma glucose; altered distribution and proper functioning of other nutrients including iron, sulfur amino acids, vitamin B₁₂, pyridoxine, and folic acid
- **Sheep** — Depressed growth, total serum protein, erythrocyte counts, ruminal urease activity, total hepatic lipids, cholesterol; altered tissue distribution of copper and iron

**Speculated Importance for Humans:**

Because nickel can affect sulfur amino acid, vitamin B₁₂, pyridoxine, and folic acid metabolism in animals; nickel nutriture might have an effect on the association between homocysteine and cardiovascular disease in humans

**Predisposing Factors for Deficiency:**

Low dietary protein, inadequate dietary iron, high dietary simple sugars, and stressors that alter sulfur amino acid or labile methyl metabolism including vitamin B₁₂, vitamin B₆, and folic acid deficiency, and homocysteine supplementation

**Postulated Adequate Intake for Humans:**

Based on animal studies, should be less than 100 μg/day; a nickel requirement of 25-35 μg/day has been suggested

**Food Sources:**

Nuts, leguminous seeds (e.g., beans, peas), pulses, grains, chocolate
### TABLE 71.14
Silicon. Biological Function in Lower Forms of Life, Deficiency Signs in Animals, and Speculated Importance and Postulated Adequate Intake for Humans

**Biological Function in Lower Forms of Life:**

Silicon is a component of body structure in some primitive classes of organisms including diatoms (unicellular plants), radiolarians, and some sponges; affects gene expression in diatoms.

**Possible Biological Function in Humans:**

Structural or other function that influences bone cartilage composition and ultimately calcification; needed for proper collagen formation

**Deficiency Signs in Experimental Animals:**

- **Chick** — Skull structure abnormalities associated with depressed collagen content; long bone abnormalities characterized by small, poorly formed joints; defective endochondral bone growth associated with depressed contents of articular cartilage, water, hexosamine, and collagen
- **Rat** — Increased humerus hexose; decreased humerus hydroxyproline, femur alkaline and acid phosphatase, and plasma ornithine aminotransferase activity (a key enzyme in collagen synthesis); altered plasma and amino acid and bone mineral composition

**Speculated Importance for Humans:**

Needed for the initiation of bone calcification and thus proper bone growth and remodeling; needed for proper wound healing

**Predisposing Factors for Deficiency:**

- Inadequate dietary calcium and excessive dietary aluminum

**Postulated Adequate Intake for Humans:**

On the basis of animal data, the human requirement, if silicon is highly available, would be about 2 to 5 mg/day. However, on the basis of balance data, a silicon intake of 30 to 35 mg/day was suggested for athletes, which was 5 to 10 mg higher than that suggested for nonathletes.

**Food Sources:**

- Unrefined grains of high fiber content and cereal products
TABLE 71.15
Vanadium: Biological Function in Lower Forms of Life, Deficiency Signs in Animals, and Speculated Importance and Postulated Adequate Intake for Humans

Biological Function in Lower Forms of Life:
Vanadium is an essential cofactor for some nitrogenases which reduce nitrogen gas to ammonia in bacteria, and for bromoperoxidase, iodoperoxidase and chloroperoxidase in algae, lichens, and fungi, respectively. The haloperoxidases catalyze the oxidation of halide ions by hydrogen peroxide, thus facilitating the formation of a carbon-halogen bond.104

Possible Biological Function in Humans:
Vanadium may have a role in optimal thyroid hormone function.

Deficiency Signs in Experimental Animals:
Goat — Depressed milk production and life span; increased rate of spontaneous abortion; death, sometimes preceded by convulsions, between ages 7 and 91 days; skeletal deformities in the forelegs; thickened forefoot tarsal joints
Rat — Increased thyroid weight and thyroid weight/body weight ratio; decreased erythrocyte glucose-6-phosphate dehydrogenase and cecal total carbonic anhydrase; altered response to high and low dietary iodide

Speculated Importance for Humans:
Identification of a specific biochemical function for vanadium is necessary to disentangle pharmacologic from nutritional findings. Otherwise, the possible nutritional importance of vanadium is unclear. Because vanadium is so pharmacologically active, a beneficial pharmaceutical role for this element might be found; this includes as a treatment for diabetes105,106 and as an anti-tumorigenic substance.103

Predisposing Factors for Deficiency:
Stressors that change thyroid status or iodine metabolism; factors reducing absorption including high iron, aluminum hydroxide, and chromium

Postulated Adequate Intake for Humans:
Based on animal data, a daily dietary intake of 10 µg probably would meet the postulated human requirement for vanadium. To date, pharmacologic doses used to experimentally treat diabetes, e.g., 100 mg/day of vanadyl sulfate, 125 mg/day of sodium orthovanadate, and 50 mg vanadium/day as vanadyl sulfate, have not been established as safe or nontoxic.

Food Sources:
Shellfish, mushrooms, prepared foods, whole grains
cadmium, fluorine, germanium, lead, lithium, rubidium, and tin. The information in Table 71.16 comes from reviews by Nielsen.72,95,98,108

Summary
It is likely that not all the essential mineral elements for humans have been identified. Biochemical functions have not been established for some mineral elements. Except for iodine and iron, the full extent of the pathological consequences of marginal or deficient intakes of the trace and ultratrace elements has not been established, which makes it
<table>
<thead>
<tr>
<th>Element</th>
<th>Deficiency Signs (Experimental Animals)</th>
<th>Usual Daily Dietary Intakes</th>
<th>Food Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>Chick — Depressed growth&lt;br&gt;Goat — Depressed growth and life expectancy, increased spontaneous abortions, incoordination and weakness in hind legs</td>
<td>2-10 mg</td>
<td>Baked goods prepared with chemical leavening agents, grains, vegetables, tea</td>
</tr>
<tr>
<td>Bromine</td>
<td>Goat — Depressed growth, fertility, milk fat production, hematocrit, hemoglobin, and life expectancy; increased spontaneous abortions</td>
<td>2-8 mg</td>
<td>Grains, nuts, fish</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Goat — Depressed growth&lt;br&gt;Rat — Depressed growth</td>
<td>19.20 µg</td>
<td>Shellfish, grains, leafy vegetables</td>
</tr>
<tr>
<td>Fluorine</td>
<td>Goat — Depressed growth and life span; histological changes in kidney and endocrine organs&lt;br&gt;Rat — Depressed growth; altered incisor pigmentation</td>
<td>Fluoridated water areas 1.3 mg; Nonfluoridated water areas 0.3-0.6 mg</td>
<td>Fish, tea, fluoridated water</td>
</tr>
<tr>
<td>Germanium</td>
<td>Rat — Decreased tibial DNA; altered bone and liver mineral composition</td>
<td>0.4-3.4 mg</td>
<td>Vegetables, wheat bran, leguminous seeds</td>
</tr>
<tr>
<td>Lead</td>
<td>Pig — Depressed growth; elevated serum cholesterol, phospholipids, and bile acids&lt;br&gt;Rat — Depressed growth, liver glucose, triglycerides, LDL-cholesterol, phospholipids, glutamic-oxalacetic transaminase activity, and glutamic-pyruvate transaminase activity, and blood catalase; increased liver cholesterol and alkaline phosphatase activity and serum ceruloplasmin; anemia</td>
<td>15-100 µg</td>
<td>Seafood, food from plants grown under high-lead conditions</td>
</tr>
<tr>
<td>Lithium</td>
<td>Goat — Depressed fertility, birth weight, lifespan, liver monoamine oxidase activity, and serum isocitrate dehydrogenase, malate dehydrogenase, aldolase, and glutamine dehydrogenase activities; increased serum creatine kinase activity</td>
<td>200-600 µg</td>
<td>Meat, eggs, fish, milk, milk products, processed meats, potatoes, vegetables (content varies with geological origin)</td>
</tr>
<tr>
<td>Rubidium</td>
<td>Goat — Depressed growth, food intake, and life expectancy; increased spontaneous abortions</td>
<td>1-5 mg</td>
<td>Fruits, poultry, fish, vegetables (especially asparagus), coffee, tea</td>
</tr>
<tr>
<td>Tin</td>
<td>Rat — Depressed growth, feed efficiency, and response to sound; altered mineral composition of heart, tibia, muscle, spleen, kidney, and lung</td>
<td></td>
<td>Canned foods</td>
</tr>
</tbody>
</table>

difficult to tabulate deficiency signs and symptoms for humans. Some mineral elements, in addition to fluoride and lithium, are being found to have therapeutic value against disease. Thus, the tables in this section are works in progress and can rapidly change because of ongoing research. This research suggests that the mineral elements are of more practical nutritional concern than currently acknowledged.
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