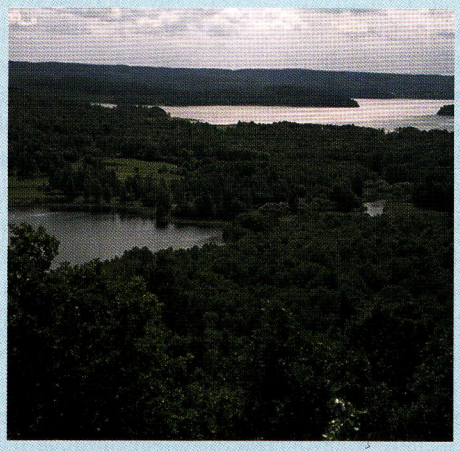

CHAPTER 7

GEOLOGICAL IMPACTS ON NUTRITION

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CONTENTS

I. GEOLOGICAL SOURCES OF NUTRIENTS

Humans, like all living organisms, biosynthesize the proteins, nucleic acids, phospholipids, and many of the smaller molecules on which they depend for life functions. The health and well-being of organisms also depend on their ability to obtain from external chemical environments a number of compounds that they cannot synthesize, at least at rates sufficient to support those functions. Thus, of the large set of bioactive compounds and metabolites called "nutrients," some are referred to as "essential" because they must be obtained from the air (oxygen), water, and diet. These include vitamins, some fatty acids, some amino acids, and several mineral elements. Foods contain essential nutrients as a result of the capacity of plants, and in some cases food animals, to synthesize and/or store them. The human body, therefore, consists of substantial amounts of "mineral elements" (see Table I) obtained mostly from such foods. (The term mineral elements is used by nutritionists and is equal to "elements" in the other chapters of this book.) These elements, of course, cannot be biosynthesized; ultimately, they are obtained from soils and, in turn, from the parent materials from which soils are derived. Therefore, good mineral nutrition is, in part, a geologic issue.

Nutritionally important mineral elements include some (e.g., manganese [Mn]) that occur predominately in silicates, some (e.g., zinc [Zn], selenium [Se]) that occur in silicates and sulfides, some (e.g., copper [Cu], molybdenum [Mo]) that occur in sulfides or as native elements with iron (Fe), and some (e.g., iron) that occur in silicates, sulfides, and as the native metal. The most abundant of these is iron, which is the fourth most abundant element in the Earth's crust (see also Chapter 2, this volume).

About 22 mineral elements are known or suspected to be essential for humans and other animals (see Table II). Some are required in fairly large amounts, grams per kilogram of diet, and are therefore referred to as "macronutrients"; others are required in much smaller amounts, e.g., microgram-to-milligrams per kilogram

TABLE I. Nutritionally Essential Mineral Elements in the Human Body

Element	*Typical amount*[a]
Ca	1000 g
P	700 g
Mg	20–28 g
Na	1.3 g
K	110–150 g
Mg	20–28 g
Zn	2–2.5 g
Cu	120 mg
Se	20 mg

[a]70-kg reference.

of diet and are referred to as "micronutrients." At least eight mineral elements function physiologically in their simple cationic forms (Ca^{+2}, Mg^{+}, Na^{+}, K^{+}, Fe^{+2}, Cu^{+2}, Zn^{+2}, and Mn^{+}) and can, therefore, be subject to chelation by either intact proteins or a variety of small, organic molecules. Some chelates (e.g., the heme moiety in hemoglobin and myoglobin) are essential in metabolism; some (e.g., amino acids, EDTA) facilitate the absorption, transport, and tissue storage of mineral ions; and others (e.g., phytic acid, oxalic acid) can interfere with the enteric absorption of certain essential cations. For example, the transition metal ions (Fe^{+2}, Cu^{+2}, and Zn^{+2}) form coordinate covalent bonds with ligands containing the electron-donor atoms N, S, and O, the histidinyl imidazole-N (Cu^{+2}), the cysteinyl sulfhydryl-S (Zn^{+2}), and the aspartyl and glutamyl carboxyl-O (Fe^{+2}, Cu^{+2}, and Zn^{+2}). Three mineral ele-

TABLE II. Mineral Elements Known and Suspected to be Essential for Optimal Health

Accepted essentials[a]	*Suspected essentials*[b]	*Known or implicated functions*
Macronutrient elements		
Ca		Bone structure, nervous transduction
P		Bone structure, membrane structure, metabolic regulation
Mg		Bone structure, electrochemical regulation, enzyme catalysis
Na		Electrochemical regulation, acid-base balance, osmotic control of water distribution
K		Electrochemical regulation, acid-base balance, osmotic control of water distribution
Cl		Electrochemical regulation; acid-base balance, osmotic control of water distribution
Micronutrient elements		
Fe		Oxygen transport, electron transport
Cu		Enzyme catalysis
Zn		Enzyme catalysis, protein structure
I		Metabolic regulation
Se	Ni	Enzyme catalysis, antioxidant protection, redox regulation, anti-tumorigenic metabolites
Mn	Pb	Enzyme catalysis
Mo	As	Potentiation of insulin action in the maintenance of glucose tolerance
Cr	B	Enzyme catalysis
F	V	Protects against dental caries
Co[c]	Si	Single carbon metabolism as active center of the vitamin B_{12} molecule
		Fetal survival and anemia in experimental animals
		Anemia in experimental animals
		Reproductive function and growth in experimental animals
		Bone mineralization in experimental animals
		Growth in experimental animals
		Reproductive function and fetal development in animals, calcification in cell culture

[a]Essentiality demonstrated on the basis of specific biochemical functions.
[b]Essentiality indicated by physiological impairment correctable by supplementation.
[c]The element itself can be used only by ruminants with foregut microflora capable of synthesizing that vitamin. For this reason, Co is considered essential only for ruminants, while the essential form for all non-ruminants including humans is vitamin B_{12}.

ments function as anions or in anionic groupings (Cl^-, PO_4^{-3}, MoO_4^{-2}). Two, iodine [I] and selenium, are nonmetals and function in covalent compounds (e.g., iodothyronine, selenocysteine) formed metabolically. The biologic significance of these elements, therefore, tends to be a property of their particular organic species rather than of the element per se.

II. MINERAL ELEMENTS NEEDED FOR GOOD HEALTH

Sixteen mineral elements are established as being essential for good health (Table II). These, collectively, have five general physiological roles:

1. Bone and membrane structure: calcium, phosphorus, magnesium, fluoride
2. Water and electrolyte balance: sodium, potassium, chloride
3. Metabolic catalysis: zinc, copper, selenium, magnesium, molybdenum
4. Oxygen binding: iron
5. Hormone effects: iodine, chromium

Although some of these functions are effected by the mineral ions themselves, many are effected by macromolecules in which one or more minerals are bound, either covalently or otherwise. Because these are all critical life functions, the tissue levels of many nutritionally essential mineral elements tend to be regulated within certain ranges despite varying levels of intake by homeostatic control of enteric absorption and tissue storage and/or excretion. For mineral cations such as Cu^{+2} and Zn^{+2}, regulation occurs primarily at the level of enteric absorption. For mineral elements that tend to be highly absorbed (e.g., selenium, boron), homeostasis is achieved by control at the level of excretion, i.e., through the urine, bile, sweat, and breath. In the case of iron, access to active forms is regulated by altering the storage of the element in an inactive form, e.g., ferritin. The ability to orchestrate these physiological processes to achieve homeostatic control of cellular access to such mineral elements is an important factor in ameliorating the effects of short-term dietary deficiencies or excesses.

Calcium—The human body contains more than 1 kg of calcium [Ca] 99% of which is in the skeleton where it serves as the dominant cationic component (26% of dry weight). Bone mineral consists of a complex matrix of plate-like crystals laid down by osteoblasts in or along collagen fibrils in several solid phases: hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$), whitlockite ($[Ca,Mg]_3[PO_4]_2$), amorphous $Ca_9(PO_4)_6X$, octacalcium phosphate ($Ca_8H_2[PO_4]_6$-H_2O), and brushite ($CaHPO_4$-$2[H_2O]$). Bone calcium is in constant turnover, with mineralization and mobilization of bone minerals occurring continually in the healthy bones of both children and adults. This "remodeling" allows the bone to serve as a source of calcium for noncalcified tissues, which mitigates against irregularities in day-to-day calcium intakes. Such homeostatic control maintains calcium in the ranges of 8.5–10.5 $mg\,dl^{-1}$ in plasma and of 45–225 $mg\,kg^{-1}$ intracellularly. These levels are regulated by vitamin D metabolites (e.g., 1,25-dihyroxycholecalciferol), which affect the active transport of calcium across the gut, the recovery of calcium by the renal tubule, and the remodeling of bone in processes also involving parathyroid hormone, calcitonin, and estrogen (Hollick, 1994; Jones et al., 1998). Only a small fraction of intracellular calcium exists in the ionic form, Ca^{+2}, which functions as a second messenger to signal many key cellular events, e.g., cell volume regulation, fertilization, growth-factor-induced cell proliferation, secretion, platelet activation, and muscle contraction. Therefore, a key aspect of cell regulation is the control of the release of the Ca^{+2} signal. In various cells, this process is thought to involve 1,4-inositoltriphosphate or nervous stimulation as triggers and protein kinase C and cyclic AMP as inhibitors (Bronner, 1997). Impaired bone mineralization in young children results in deformities of the growing bones and is called rickets; in adults with formed bone it is called osteomalacia and is characterized by increase fracture risk and loss of stature. Conditions of either type can be caused by insufficient intakes of calcium, vitamin D (or exposure to sunlight which is necessary for the biosynthesis of the vitamin), phosphorus and/or magnesium. Only in very severe deficiency, when bone mineral has largely been exhausted, does calcium deficiency result in impaired nervous conduction or muscular contraction. Excessive calcium intake, which typically occurs due to the inappropriate use of calcium supplements, can lead to renal stone formation, hypercalcemia, and renal insufficiency as well as impaired utilization of iron, zinc, magnesium, and phosphorus.

Phosphorus—The human body contains approximately 700 g of phosphorus, about 85% of which is in bones where it serves a structural function in bone minerals (see also Chapter 28, this volume). Much of the nearly 14% of body phosphorus in noncalcified tissues also serves a structural function in the phospholipids that comprise plasma and subcellular membranes

(Berner, 1997). As phosphate, the element phosphorus is also important in metabolism because it is incorporated into nucleic acids, RNA, DNA, proteins (including transcription factors), ATP, and numerous other high-energy substrates. Intracellular phosphate serves as a regulator of glycolysis, a key pathway for rendering oxygen available to the tissues; and phosphoproteins play essential roles in the electron-transport system of mitochondria, which generates metabolically useful energy from carbohydrates and lipids. Other phosphoproteins serve as cellular growth factors and cytokines. Like calcium, phosphorus homeostasis is affected by the vitamin D hormone system. Deficiency of phosphorus (hypophosphatemia) can result in tissue hypoxia due to the loss of erythrocyte 2,3-diphosphoglucose and ATP, which leads to nervous signs (convulsions, confusion), renal dysfunction, and smooth muscle problems (e.g., dysphagia, gastric atony). Hypophosphatemia can also result in rickets and osteomalacia. Chronic, excessive intakes of phosphorus can cause hyperphosphatemia which leads to interference with calcium homeostasis, bone demineralization, and ectopic calcification of the kidney.

Magnesium—The human body typically contains 20–28 g of magnesium, which is widely distributed: 60–65% of that amount is in bone, 25–30% in muscle, and the balance is in other tissue and extracellular fluid. In fact, Mg^{+2} is second only to K^+ as the most abundant intracellular inorganic cation. Normal plasma Mg concentrations are in the range of 0.65–0.88 mmol L^{-1}. Magnesium tends to be well absorbed (i.e., at rates of 67–70%) by a saturable process as well as simple diffusion. Amounts of the element not retained for tissue growth/turnover are excreted in the urine. The cation, Mg^{+2}, functions as a cofactor in at least 300 enzymatic reactions (Shils, 1997). These include virtually all kinase reactions (in which Mg^{+2} complexes with the negatively charged ATP^{-4} to form the substrate), pyrophosphotransferases, acyl-CoA synthetases, and adenylate cyclase. The cation is also involved in the regulation of ion movements within cells. Magnesium deficiency (hypomagnesemia) is characterized by neuromuscular signs (hyperactivity, muscle spasms, tremor, weakness) and gastrointestinal symptoms (anorexia, nausea, vomiting). Magnesium has a cathartic effect, but adverse effects have been identified only for magnesium ingested from non-food sources.

Sodium—The human body contains approximately 1.3 g of sodium [Na], 90% of which is in the extracellular space where it serves as one of the three (with K^+ and Cl^-) osmotically active solutes in extracellular fluid. Sodium is freely and quantitatively absorbed, but the element is homeostatically regulated within a normal range of 135–145 mmol L^{-1} at the level of renal reabsorption effected by renin, angiotensin, aldosterone, antidiuretic hormone, atrial natriuretic peptide, and other factors affecting renal blood flow (Harper et al., 1997). Intracellular Na^+ is normally maintained at relatively low levels. The Na^+ gradient is used as an energy source for the uphill transport of a variety of solutes (e.g., amino acids, Ca^{+2}, Mg^{+2}, H^+) into the cell. The maintenance of the Na^+ gradient is maintained by several transport systems including the Na^+–K^+ pump which effects the ATP-dependent anti-transport of Na^+ (in) and K^+ (out), the Na^+–H^+ exchanger, Na^+–K^+–Cl^- co-transporters, the Na^+–Ca^{+2} exchanger, Na^+–Mg^{+2} exchangers, and the voltage-regulated Na^+ channel. Sodium deficiency results in muscle cramps, headache, poor appetite, and dehydration, but the main sign is fatigue.

Potassium—Potassium (K) is the most abundant cation in the human body, with total body stores typically in the range of 110–150 g. In contrast to Na^+, K^+ is found primarily (98%) in the intracellular compartment; most cells contain about 150 mM K^+, while the level in extracellular fluid is only about 4 mM. Potassium is freely absorbed, with homeostasis affected by rapid renal excretion. Potassium passes the plasma membrane into cells by the Na^+,K^+-ATPase, the H^+,K^+-ATPase, the Na^+–$2Cl^-$–K^+ co-transporter, and K^+ conductance channels. Increases in extracellular K^+ concentrations can be caused by vigorous exercise leading to K^+ efflux from myocytes and mediating vasodilation and increased blood flow. Such increases stimulate the release of catecholamines and insulin, which stimulates K^+ uptake via the Na^+,K^+-ATPase (Peterson, 1997). Potassium deficiency (hypokalemia) can be caused by insufficient intake and/or excessive excretion (e.g., due to diarrhea, bulimia) of the element. This is characterized by skeletal muscular weakness; smooth muscle paralysis resulting in anorexia, nausea, vomiting, and constipation; cardiac arrhythmias; carbohydrate intolerance due to diminished insulin secretion; impaired renal function due to reduced blood flow; and altered water balance involving increased water consumption secondary to elevated angiotensin II levels.

Chloride—Chloride (Cl^-) is the major extracellular anion maintained at a concentration of 100–110 mmol L^{-1} in that fluid. Like Na^+, there is no control over Cl^- absorption, and homeostasis is affected by renal reabsorption/elimination. The transport and cellular uptake of Cl^- is effected by a number of transporters including a K^+–Cl^- co-transporter, a Na^+–K^+–$2Cl^-$ co-transporter,

Cl^-–HCO_3 exchangers, cystic fibrosis transmembrane conductance regulator (mutation of this causes cystic fibrosis), Ca^{+2}-activated Cl^- channels, voltage-regulated Cl^- channels, and mechanically activated Cl^- channels (Harper et al., 1997).

Iron—The human body typically contains approximately 5 g of iron, and its metabolic function is to transport oxygen and electrons. Iron serves as the redox agent in a large number of enzymatic reactions involving substrate oxidation and reduction. These include oxidoreductases (e.g., xanthine oxidase/dehydrogenase), monooxygenases (e.g., amino acid oxidases, cytochrome P-450), and dioxygenases (e.g., amino acid dioxygenases, lipoxygenases, peroxidases, fatty acid desaturases, nitric oxide synthases) (Beard & Dawson, 1997). Iron homeostasis is effected at the level of enteric absorption. Dietary iron generally exists in either heme (from hemoglobin and myoglobin in animal products) or non-heme (i.e., organic and inorganic salts in plant-based and iron-fortified foods) forms, each of which is absorbed by a different mechanism. Heme iron is much better absorbed and less affected by enhancers and inhibitors of absorption than non-heme iron, which is strongly regulated by the intestinal mucosal cells in response to iron stores and blood hemoglobin status. Thus, iron-adequate men and women typically absorb about 6 and 13% of dietary iron, respectively, with non-heme iron absorption as great as 50% under conditions of severe iron-deficiency anemia. Excess absorbed iron is stored as ferritin and hemosiderin in the liver, reticuloendothelial cells, and bone marrow. The loss of iron from the body is very low, about 0.6 mg per day, and is primarily due to losses in the bile and exfoliated mucosal cells eliminated in the feces. Menstrual losses can be significant, as can nonphysiological losses resulting from parasitism, diarrhea, and enteritis, which are thought to account for half of the cases of global iron-deficiency anemia. Iron deficiency is manifested as hypochromic, normocytic anemia; lethargy; apathy; listlessness; fatigue; impaired non-shivering thermogenesis; impaired immune function; impaired cognitive development; and reduced physical performance. In pregnancy, iron-deficiency increases the risk of premature delivery, low birth weight, and infant and maternal mortality.

Epidemiologic observations have linked high dietary iron intakes or high iron stores with increased risk of coronary heart disease (Salonen et al., 1992). The toxic potential of iron arises from its pro-oxidative effects, which yield reactive oxygen species that attack polyunsaturated membrane lipids, proteins, and nucleic acids. An iron-overload disease, hereditary hemochromatosis, is caused by a defect in the regulation of iron absorption, which leads to very high circulating transferrin iron. Clinical signs appear when body iron accumulates to about tenfold excess of normal: these include hepatic cirrhosis, diabetes, heart failure, arthritis, and sexual dysfunction.

Zinc—The human body contains 2–2.5 g of zinc: just over half (55%) of which is in muscle, 30% in bone, with the balance distributed in other tissues. Zinc is absorbed by both carrier-mediated and simple diffusion processes which render the element only moderately absorbed (about 30%) at nutritionally adequate intakes and more efficiently absorbed under deficient conditions (Chesters, 1997). Both processes can be effected by the presence of chelating substances that may promote (e.g., meats) or impair (e.g., phytic acid) zinc absorption. Zinc homeostasis is also affected by the regulation of zinc excretion/reabsorption in and from pancreatic and intestinal secretions; urinary losses of zinc are low and not generally responsive to changes in zinc intake. Plasma zinc levels, comprising 0.1% of total body zinc, are not regulated and are therefore not indicative of overall zinc status except under conditions of marked deficiency. Zinc has been shown to function in at least 50 widely varied enzymes. In each, the element serves either in a catalytic (i.e., at the active site), a co-catalytic (i.e., near the active site), or a structural role bound most commonly to histidinyl, glutamyl, or aspartyl residues. Zinc deficiency is manifested as losses in activities of at least some zinc enzymes (e.g., some dehydrogenases, alkaline phosphatase, superoxide dismutase), although direct links between such losses and the physiologic manifestations of zinc deficiency have not been established. Zinc deficiency is characterized by poor growth and dwarfism, anorexia, parakeratotic skin lesions, diarrhea, impaired testicular development, impaired immune function (including wound healing), and impaired cognitive function. Low zinc status is also thought to increase risk to osteoporosis and susceptibility to oxidative stress. Very high intakes of zinc, which have occurred due to inappropriate use of zinc supplements, can interfere with copper metabolism and deplete the body of copper. Chronic exposure to excess zinc (more than $100\,mg\,d^{-1}$) can reduce immune function and HDL cholesterol.

Copper—The human body contains approximately 120 mg of copper, which is widely distributed in many tissues and fluids at $mg\,kg^{-1}$ or $\mu g\,kg^{-1}$ concentrations. Copper serves as a cofactor for a number of oxidase enzymes including lysyl oxidase, ferroxidase (ceruloplasmin), dopamine beta-monooxygenase, tyrosinase, alpha-amidating monooxygenase, cytochrome *c* oxidase,

and superoxide dismutase (Harris, 1997). These enzymes are involved in generating oxidative energy, stabilizing connective tissue matrices, maintaining iron in the ferrous (Fe^{+2}) state, synthesizing neurotransmitters, pigmenting hair and skin, supporting immune competence, and protecting the body from reactive oxygen species. Copper also functions non-enzymatically in angiogenesis, neurohormone release, oxygen transport, and the regulation of genetic expression. Copper homeostasis is effected at the level of enteric absorption. It is absorbed by facilitated diffusion (involving either specific transporters or nonspecific divalent metal ion transporters on the brush-border surface) and is transported to the liver where it is re-secreted into the plasma bound to ceruloplasmin. The element is excreted in the bile; only very small amounts are lost in the urine. Copper absorption/retention varies inversely with the level of copper intake, and tends to be moderate (e.g., 50–60%) even at low copper intakes. Copper deficiency is manifested as hypochromic, normocytic or macrocytic anemia; bone abnormalities resembling osteoporosis or scurvy; increased susceptibility to infection; and poor growth. The ingestion of high amounts of copper can cause nausea. Chronic high copper intake can lead to the hepatic accumulation of copper, which has been suspected in juvenile cases of hepatic cirrhosis in India.

Iodine—The human body contains approximately 5 mg of iodine, which functions only in the iodine-containing thyroid hormones. These include the tetraiodinated protein thyroxine (T_4) that is converted by a single deiodination to yield the active thyroid hormone triiodothyronine (T_3). The latter functions as a regulator of growth and development by increasing energy (ATP) production and activating or inhibiting the synthesis of various proteins (Hetzel & Wellby, 1997). Organic forms of iodine are converted in the upper gastrointestinal tract to the iodide anion (I^-), which is rapidly and almost completely absorbed. In contrast, when T_3 is ingested, about 80% is absorbed intact. Absorbed I^- circulates in the plasma in the free ionic form and is rapidly removed by the thyroid and kidney. Iodine homeostasis is effected at the level of the kidney, and urinary excretion is the major route of loss (comprising 90% of iodine absorbed by iodine-adequate individuals). The deiodination of T_4 occurs in the thyroid, skeletal muscles, and brain, but the thyroid gland is the only storage site for iodine where it appears mostly as mono- and diiodotyrosine and T_4, with a small amount of T_3. Iodine deficiency in adults is characterized as thyroid hypertrophy or goiter and in children as myxedematous cretinism. Collectively, these iodine deficiency diseases comprise a global health problem, and cretinism is the greatest source of preventable mental retardation (see also Chapter 16, this volume).

Selenium—The human body typically contains approximately 20 mg of selenium. This is widely distributed in all tissue in which the element is bound to proteins. Some selenium-containing proteins contain the element in the form of the amino acid selenocysteine (SeCys). Selenoamino acid cannot be incorporated into peptides during protein synthesis (SeCys cannot charge the tRNA for cysteine); instead it is synthesized by a unique co-translational process encoded by a codon (UGA) that otherwise signals termination (Sunde, 1997). When consumed as selenomethionine (SeMet), a large number of other proteins can incorporate selenium nonspecifically, due to the mimicry of SeMet with its sulfur-containing analogue in general protein synthesis. Because foods contain both of the selenoamino acids, human tissues typically contain both the specific and nonspecific selenoproteins. Only the former have physiological functions and these include: multiple isoforms of glutathione peroxidase, thioredoxin reductase, and iodothyronine 5′-deiodinase, as well as an enzyme involved in SeCys synthesis, selenophosphate synthase, and at least four selenoproteins of unknown function. As essential constituents of these SeCys proteins, selenium functions in antioxidant protections, redox regulation, and thyroid hormone regulation. It is not clear whether uncomplicated selenium deficiency (i.e., not accompanied by other deficiencies or oxidative stress) results in significant physiological impairment. Severely low selenium intakes (greater than 20 $\mu g\,d^{-1}$) have been associated with juvenile cardiomyopathy in China (Keshan disease), which also appears to have a viral component to its etiology.

Recent interest in selenium centers around the apparent efficacy of supranutritional intakes of the element to reduce cancer risk. A decade-long, randomized, double-blind, placebo-controlled clinical intervention trial found that supplementation of free-living American adults with 200 $\mu g\,d^{-1}$ selenium (in addition to their normal diets) reduced major cancer incidence by half or more (Clark et al., 1996). Similar effects have been shown in animal studies. Current thinking is that a normal metabolite of selenium can stimulate apoptosis in transformed cells (Combs & Lu, 2001). Selenium intakes greater than 1 $mg\,d^{-1}$ can induce dermatological changes, including brittle hair and nails. Chronic intake approaching 5 mg has been reported to lead to skin rash, paresthesia, weakness, and diarrhea (see also Chapter 15, this volume).

Manganese—Manganese (Mn) functions as a cofactor for enzymes in antioxidant defense (mitochondrial superoxide dismutase), gluconeogenesis (pyruvate carboxylase, phosphoenol–pyruvate carboxykinase), glycoprotein biosynthesis (glycosyl transferases), nitrogen metabolism (arginase, glutamine synthase), and cholesterol biosynthesis (farnesyl pyrophosphate synthetase). Little is known about the mechanisms of absorption, transport, or cellular uptake of manganese, although the element is widely distributed in noncalcified tissues with the greatest concentrations in the liver (Leach & Harris, 1997). The greatest route of manganese excretion appears to be the bile in which it is released in bound form. There is little available evidence of manganese deficiency in humans, although studies in experimental animals have shown effects on fetal survival, normal skeletal development (i.e., shortened limbs, twisted legs, lameness), ataxia, glucose tolerance, and hepatic steatosis.

Molybdenum—Molybdenum (Mo) functions as the active center of three enzymes that catalyze oxidative hydroxylations: sulfite oxidase (the last step in the degradation of sulfur amino acids), xanthine dehydrogenase, and aldehyde oxidase (which transfers electrons to other redox cofactors and, ultimately, to cytochrome *c*, molecular oxygen, or NAD^+). In these enzymes, the element is found in a pterin-containing, molybdenum cofactor, the synthesis of which in eukaryotes remains poorly understood (Johnson, 1997). Molybdenum appears to be efficiently absorbed at all levels of intake, apparently by a passive process. It is transported in the blood attached to proteins in erythrocytes. Whole blood molybdenum levels vary directly with dietary molybdenum intake, although plasma Mo^+ levels are maintained at about 5 nmol L^{-1}. Molybdenum is widely distributed in the body, with greatest concentrations in liver, kidney, adrenal gland, and bone. One human case of molybdenum deficiency has been described; signs (all of which responded to molybdenum therapy) included tachycardia, tachypnea, severe headache, night blindness, nausea, and vomiting.

Chromium—Chromium (Cr) potentiates the action of insulin and has been shown to restore glucose tolerance in malnourished infants. Several studies have shown that chromium supplementation lowers circulating glucose levels, increases plasma insulin, and produces a favorable profile of plasma lipids (Offenbacher et al., 1997). It has been suggested that these effects may be due to a low molecular weight chromium-binding substance that may amplify insulin receptor tyrosine kinase activity in response to insulin. Chromium can also bind to one of the binding sites of transferrin, and it has been proposed that excessive iron storage in hemochromatosis may interfere with the transport of chromium to contribute to the diabetes associated with that disorder. The enteric absorption of the element, which is absorbed as Cr^{+3}, is very low (usually no more than 2%) and appears to be regulated. Absorbed chromium accumulates in the liver, kidney, spleen, and bone.

Fluoride—Fluoride (F^-) is the ionic form of fluorine. It is very highly electronegative and reacts reversibly to hydrogen to form hydrogen fluoride which freely diffuses across the intestine, dissolves in the blood, and is taken up by the tissues where its high affinity for calcium causes it to accumulate in calcified tissues. Fluoride can stimulate new bone formation; when present in oral fluids, F^- exerts cariostatic effects due to enhanced remineralization of dental enamel and reduced acid production of plaque bacteria (Chow, 1990; Cerklewski, 1997). Prior to the widespread use of F^- in dental products and water supplies, most studies showed that the incidence of dental caries (in both children and adults) was 40–60% lower in areas with drinking water F^- concentrations of at least 0.7 mg L^{-1} when compared to communities with lower F^- levels. Excessive F^- intake can cause fluorosis of the enamel and bone. Although the former is a largely cosmetic effect involving the mottling of the teeth, skeletal fluorosis is associated with joint stiffness, calcification of ligaments, and some osteosclerosis of the pelvis and vertebrae (see also Chapter 12, this volume).

III. DIETARY SOURCES OF ESSENTIAL MINERAL ELEMENTS

Mineral elements are metabolized and, to varying degrees, stored by plants and animals, some of which constitute important sources of those elements in human diets (see Table III). That the mineral elements are not homogeneously distributed among various types of foods is clear: few foods other than dairy products are rich in calcium; sea foods constitute the best sources of iodine and chloride; meats are the most important sources of iron; and protein-rich foods comprise the best sources of zinc, copper, and selenium. Therefore, optimal mineral nutrition, like optimal nutrition in general, is most likely to be obtained from mixed diets based on a diverse selection of foods. Conversely, the monotonous, non-diverse, grain-based diets accessible to the poor of the developing world are likely to provide

TABLE III. Important Dietary Sources of Essential Mineral Elements

Element	*Sources*
Ca	Dairy products, fortified juices, kale, collards, mustard greens, broccoli, sardines, oysters, clams, canned salmon
P	Meats, fish, eggs, dairy products, nuts, beans, peas, lentils, grains
Mg	Seeds, nuts, beans, peas, lentils, whole grains, dark green vegetables
Na	Common table salt, seafood, dairy products, meats, eggs
K	Fruits, dairy products, meats, cereals, vegetables, beans, peas, lentils
Cl	Common table salt, seafood, dairy products, meats, eggs
Fe	Meats, seafood
Cu	Beans, peas, lentils, whole grains, nuts, organ meats, seafood (e.g., oysters, crab), peanut products, chocolate, mushrooms
Zn	Meats, organ meats, shellfish, nuts, whole grains, beans, peas, lentils, fortified breakfast cereals
Se	Meats from Se-fed livestock, sea fish, grain products, nuts, garlic, broccoli grown on high-Se soils
I	Iodized salt, sea fish, kelp
Mn	Whole grains, beans, peas, lentils, nuts, tea
Mo	Beans, peas, lentils, dark green leafy vegetables, organ meats
F	Fluoridated water

insufficient energy, protein, and minerals, especially calcium, copper, selenium, and biologically available iron and zinc. At the same time, the increasing use in industrialized countries of non-diverse eating habits is associated with prevalent insufficient intake of such minerals as calcium.

Soil can contribute to the total dietary intake of mineral elements. This can occur through adherent soil particles on foods and suspended soil particles in drinking and cooking water, as well as through the direct consumption of soil. The latter practice of geophagia can be deliberate in some communities in which the eating of clays occurs (see Geophagy and the Involuntary Ingestion of Soil, this volume). Consumption of clays with high cation-exchange capacities can provide substantial supplements of calcium, iron, copper, zinc, and manganese; other clays can interfere with the enteric absorption of iron and zinc. Consumption of iron-rich lateritic soils or waters draining them can provide enough iron to impair the utilization of copper and zinc.

In some areas, fresh water supplies can provide nutritionally important amounts of such minerals as calcium, magnesium, iron, manganese, and arsenic, and industrialized countries have used municipal water as a vehicle for providing fluoride. In a few locales surface runoff from selenium-rich soils has been found to contain biologically significant amounts of selenium, but such cases are rare and most water supplies are very low in that nutrient.

For many people in industrialized countries, fortified foods and nutritional supplements constitute important sources of several of the mineral elements. Various forms of copper, zinc, iron, and selenium are offered in over-the-counter formations, both as individual supplements as well as compounded in multivitamin mineral supplements. Calcium, typically as the carbonate or gluconate salts, is now commonly used to fortify orange and other fruit juices. Consumer response to such nutrient-fortified foods has been very strong, and this aspect of consumer retailing is expected to continue to grow.

IV. MINERAL ELEMENT BIOAVAILABILITY

For several nutrients only a portion of the ingested amount is absorbed and utilized metabolically. Therefore, it is necessary to consider this when evaluating the nutritional adequacy of foods and diets. This concept, bioavailability, is particularly important in mineral nutrition, because some foods are less useful sources of essential minerals than might be expected from their absolute mineral content.

Mineral bioavailability depends on both physiological and exogenous factors. Physiological determinants of mineral bioavailability include:

1. Age-related declines in the efficiency of enteric absorption of copper and zinc
2. Early postnatal lack of regulation of absorption of iron, zinc, and chromium
3. Adaptive increases in the absorptive efficiencies of iron and zinc, copper, manganese, and chromium by receptor upregulation during periods of deficiency
4. Dependence on other nutrients for the physiological functions of selenium and iodine in thyroid hormone metabolism, and copper and iron in catecholamine metabolism
5. Anabolic effects on tissue sequestration of zinc and selenium
6. Catabolic effects on zinc, selenium, and chromium losses

The chemical form of an element as well as the presence/absence of other factors in foods and diets can impair or enhance its absorption and post-absorptive utilization. For example, 25–30% of the heme iron in animal tissues can be absorbed, but 2–5% of the non-heme iron in plant foods is absorbed. The utilization of plant sources of iron can be markedly improved by including in the diet sources of ascorbic acid (e.g., oranges) or meats, both of which promote the utilization of non-heme iron. Similarly, citrate and/or histidine can enhance the absorption of zinc. Dietary ascorbate (vitamin C) can, thus, also enhance the antagonistic effect of iron on copper utilization.

Mineral bioavailability can be reduced by dietary factors that reduce enteric absorption. For example, phytate, phosphorus, and triglycerides can reduce the luminal solubility and, hence, the absorption of calcium. Phytate and other non-fermentable fiber components can bind zinc and magnesium, reducing the absorption of each. Sulfides can reduce the absorption of copper by similar means. Minerals that share transporters can be mutually inhibitory for absorption, e.g., sulfite and selenite, cadmium and zinc, and zinc and copper.

In general, problems related to poor bioavailability are greatest for iron in plant-based containing phytates and/or polyphenols but there are few problems with promotor substances. For calcium there are problems with bioavailability when poorly soluble forms are consumed with vegetables (spinach, rhubarb, beet greens, chard) containing inhibitory oxalates without others (artichokes) containing fructose oligosaccharide promoters; for zinc in diets high in unrefined (>90% extraction), unfermented cereal grains or high-phytate soy products, especially those fortified with inorganic calcium salts; and for selenium consumed as plant foods (containing SeMet much of which is diverted to protein synthesis). For these reasons, the utilization of these minerals as consumed in most diets tends to be moderate at best, though in each case it can be markedly enhanced through appropriate dietary choices.

V. QUANTITATIVE ESTIMATES OF MINERAL NEEDS AND SAFE EXPOSURES

Dietary standards have been set for several, but not all, of the nutritionally essential mineral elements. International standards have been developed for only some minerals (FAO-WHO, 2002) (Table IV). The most current and extensive standards are the Dietary Reference Intakes (DRSs) published by the U.S. National Academy of Science (NAS) (Food and Nutrition Board, 1997, 2000, 2001) (Table V). It is important to note that the expert panels of the respective organizations used the same primary data, i.e., the published scientific literature. Also, each based its recommendations on estimates of individual physiological need (i.e., the World Health Organization's "basal requirement" and the "recommended dietary allowance," RDA, from NAS) which was then inflated to accommodate estimated interindividual variation. This approach produced the WHO "normative requirement" and NAS "estimated average requirement" (EAR). The NAS process went further to include estimates of "average intakes" (AIs) in cases where data were not sufficient to support EARs or RDAs. Both groups also estimated safe limits of exposure: WHO created "upper limits of safe ranges of population mean intakes" (Table VI), and NAS created "upper tolerable limits" (ULs) (Table VII).

VI. CLINICAL ASSESSMENT OF MINERAL STATUS

The status assessment of the essential minerals, which vary so much in metabolic function, homeostatic regulation, and tissue distribution, calls for a mixed

TABLE IV. International Dietary Recommendations (Units per Day) for Essential Mineral Elements[a,b]

Life stage	*Ca (mg)*	*P (mg)*	*Na (mg)*	*K (mg)*	*Cl (mg)*	*Mg (mg)*	*Fe[c] (mg)*	*Cu (mg)*	*Zn[d] (mg)*	*Se (μg)*	*I (μg)*	*Mn (mg)*	*Mo (mg)*	*Cr (μg)*	*F (mg)*
Children															
0–3 months								0.33–0.55[f]							
3–6 months	300[e]					26[e]		0.37–0.62[f]	2.8[e]	6	[15][g]				
	400[f]					36[f]									
7–12 months	400					53	[9][g]	0.60	4.1	10	130				
1–3 years	500					60	6	0.58	4.8	17	75				
3–6 years	600					73	6	0.57	5.1	21	115				
6–9 years	700					100	9	0.75	5.6	21	110				
10–11 years											140f				
											135m				
10–12 years								0.77f							
								0.73m							
10–14 years							14f				140f				
							15m				135m				
12–15 years								1.00							
12–18 years											110f				
											100m				
15–18 years							31f	1.33f							
							19m	1.15m							
10–18 years	1300					230f			7.8f	26f					
						250m			9.7m	32m					
Adults															
19–50 years	1000					220f	29f	1.35f	4.9f	26f	110f				
						260m	14m	1.15m	7.0m	34m	130m				
51–65 years	1300f					220f	11f	1.35f	4.9f	26f	110f				
	1000m					260m	14m	1.15m	7.0m	34m	130m				
65+ years	1300					190f	11f	1.35f	4.9f	26f	110f				
						230m	14m	1.15m	7.0m	34m	130m				
Pregnancy															
1st trimester						220		1.15	5.5		200				
2nd trimester						220		1.15	7.0	28	200				
3rd trimester	1200					220		1.15	10.0	30	200				
Lactation															
0–3 months	1000					270	15	1.25	9.5	35	200				
3–6 months	1000					270	15	1.25	8.8	35	200				
6–12 months	1000					270	15	1.25	7.2	42	200				

[a]Recommendations for copper are normative dietary requirements, WHO (1996).
[b]Recommendations for calcium, magnesium, iron, zinc, selenium, and iodine, FAO-WHO (1998).
[c]10% bioavailability conditions.
[d]Moderate (30–35%) bioavailability conditions.
[e]Breast-fed infants.
[f]Formula-fed infants.
[g]Value expressed in units $kg^{-1} d^{-1}$.

TABLE V. Dietary Recommendations for Essential Mineral Elements (Units per Day)

Life stage	*Ca (mg)*	*P (mg)*	*Na (mg)*	*K (mg)*	*Cl (mg)*	*Mg (mg)*	*Fe (mg)*	*Cu (μg)*	*Zn (mg)*	*Se (μg)*	*I (μg)*	*Mn (mg)*	*Mo (mg)*	*Cr (μg)*	*F (mg)*
Children															
0–6 months	210[a]	100[a]	120[c]	500[c]	180[c]	30[a]	0.27[d]	200[d]	2[d]	15[e]	110[d]	0.003[d]	0.2[d]	0.2[d]	0.01[a]
7–12 mos.	270[a]	275[a]	200[c]	700[c]	300[c]	75[a]	11[f]	220[f]	3[f]	20[e]	130[d]	0.6[d]	3[d]	5.5[d]	0.5[a]
1–3 years	500[a]	460[b]	225–300[c]	1000–1400[c]	350–500[c]	80[b]	7[f]	340[f]	3[f]	20[g]	90[f]	1.2[d]	17[f]	11[d]	0.7[a]
4–8 years	800[a]	500[b]	300–400[c]	1400–1600[c]	500–600[c]	130[b]	10[f]	440[f]	5[f]	30[g]	90[f]	1.5[d]	22[f]	15[d]	1[a]
9–13 years	1300[a]	1250[b]	400–500[c]	1600–2000[c]	600–750[c]	240[b]	8[f]	700[f]	8[f]	40[g]	120[f]	1.9[d](m) 1.6[d](f)	34[f]	25[d](m) 21[d](f)	2[a]
14–18 years	1300[a]	1250[b]	500[c]	2000[c]	750[c]	410(m)[b] 360(f)[b]	11[f](m) 15[f](f)	890	11[f](m) 9[f](f)	55[g]	150[f]	2.2[d](m) 1.6[d](f)	43[f]	35[d](m) 24[d](f)	3[a]
Adults															
19–30 years	1000[a]	700[b]	500[c]	2000[c]	750[c]	400(m)[b] 310(f)[b]	8[f](m) 11[f](f)	900[f]	11[f](m) 8[f](f)	55[g]	150[f]	2.3[d](m) 1.8[d](f)	45[f]	35[d](m) 25[d](f)	4(m)[a] 3(f)[a]
31–50 years	1000[a]	700[b]	500[c]	2000[c]	750[c]	420(m)[b] 320(f)[b]	8[f](m) 11[f](f)	900[f]	11[f](m) 8[f](f)	55[g]	150[f]	2.3[d](m) 1.8[d](f)	45[f]	35[d](m) 25[d](f)	4(m)[a] 3(f)[a]
51+ years	1200[a]	700[b]	500[c]	2000[c]	750[c]	420(m)[b] 320(f)[b]	8[f]	900[f]	11[f](m) 8[f](f)	55[g]	150[f]	2.3[d](m) 1.8[d](f)	45[f]	30[d](m) 20[d](f)	4(m)[a] 3(f)[a]
>70 years	1200[a]	700[b]	500[c]	2000[c]	750[c]	420(m)[b] 320(f)[b]	8[f]	900[f]	11[f](m) 8[f](f)	55[g]	150[f]	2.3[d](m) 1.8[d](f)	45[f]	30[d](m) 20[d](f)	4(m)[a] 3(f)[a]
Pregnancy															
≥18 years	1300[a]	1250[b]				400[b]	27[f]	1000[f]	13[f]	60[g]	220[f]	2[d]	50[f]	19[d]	3[a]
19–30 years	1000[a]	700[b]				350[b]	27[f]	1000[f]	11[f]	60[g]	220[f]	2[d]	50[f]	30[d]	3[a]
31–50 years	1000[a]	700[b]				360[b]	27[f]	1000[f]	11[f]	60[g]	220[f]	2[d]	50[f]	30[d]	3[a]
Lactation															
≥18 years	1300[a]	1250[b]				360[b]	10[f]	985[f]	14[f]	70[g]	290[f]	2.6[d]	50[f]	44[d]	3[a]
19–30 years	1000[a]	700[b]				310[b]	9[f]	1000[f]	12[f]	70[g]	290[f]	2.6[d]	50[f]	45[d]	3[a]
31–50 years	1000[a]	700[b]				320[b]	9[f]	1000[f]	12[f]	70[g]	290[f]	2.6[d]	50[f]	45[d]	3[a]

[a]Average Intake (AI) value, (Food and Nutrition Board, 1997).
[b]Recommended Dietary Allowance (RDA), (Food and Nutrition Board, 1997).
[c]Estimated Minimum Requirement, (Food and Nutrition Board, 1989).
[d]Average Intake (AI) value, (Food and Nutrition Board, 2001).
[e]Average Intake (AI) value, (Food and Nutrition Board, 2000).
[f]Recommended Dietary Allowance (RDA), (Food and Nutrition Board, 2001).
[g]Recommended Dietary Allowance (RDA), (Food and Nutrition Board, 2000).

TABLE VI. International Estimates of Upper Limits (Units per Day) of Safe Intakes of Essential Mineral Elements

Life stage	*Ca (mg)*	*P (mg)*	*Na (mg)*	*K (mg)*	*Cl (mg)*	*Mg (mg)*	*Fe (mg)*	*Cu (mg)*	*Zn*[a] *(mg)*	*Se (μg)*	*I (μg)*	*Mn (mg)*	*Mo (mg)*	*Cr (μg)*	*F (mg)*
Children															
0–6 months									13						
0–12 months								(150)[b]							
1–6 years								1.5	23						
6–10 years								3.0	28						
10–12 years								6.0	32f 34m						
12–15 years								8.0	36f 40m						
15–18 years									38f 48m						
Adults															
15–60 years								12.0		400					
18–60 years									55f 45m						
Pregnancy															
General								10.0							
Lactation															
General								10.0							

[a]Moderate (30–35%) bioavailability conditions.
[b]In mcg kg^{-1}.
From WHO (1996).

approach. This approach includes elemental analyses of tissues and/or body fluids, assays of mineral-dependent enzyme activities, and measurement of functional and/or morphological indices. A battery of such tests may be feasible in research settings, but in clinical settings practicality and timeliness dictate approaches based on analyses of a single specimen of blood.

Beyond the obvious issues pertaining to sampling (i.e., number, bias, amount, homogeneity, interindividual variability, etc.), the analysis of minerals, particularly those present in only trace amounts in foods and tissues, calls for special attention to sample integrity and freedom from contamination (Milne, 2000). For example, the iron and zinc contents of plasma or serum can be affected by hemolysis; rubber stoppers and borosilicate glass can contaminate blood with zinc and boron, respectively; and some anticoagulants can produce osmotic shifts that release several elements from erythrocytes. The laboratory, too, can be a significant source of contamination: poorly treated water can contaminate with iron, calcium, magnesium, manganese, zinc, or copper; stainless steel surfaces can contaminate with chromium and nickel; and dust, paper products, wood, skin, hair, and dandruff can also be sources of contamination. For these reasons, a well-monitored laboratory designed for mineral/trace element analyses is a prerequisite for the generation of useful data.

The available methods for the clinical assessment of mineral status are presented in Table VIII, with normative values for the most practically useful of these presented in Table IX.

Status with respect to mineral elements that are active or highly regulated in circulating tissues can be assessed by analyzing their amounts in plasma/serum or blood cells (Sauberlich, 1999). For example, knowledge of plasma/serum potassium or erythrocyte iron levels can be highly informative, because those elements exert their physiological functions in those respective compartments. This is not the case for mineral elements that function in other compartments and/or chemical forms. For example, analyses of chromium, copper, or

TABLE VII. Estimated Upper Tolerable Intakes of Essential Mineral Elements (Units per Day)

Life stage	*Ca (mg)*	*P (mg)*	*Na (mg)*	*K (mg)*	*Cl (mg)*	*Mg (mg)*	*Fe (mg)*	*Cu (mg)*	*Zn (mg)*	*Se (μg)*	*I (mg)*	*Mn (mg)*	*Mo (mg)*	*Cr (μg)*	*F (mg)*
Children															
0–6 months									4[c]	45[b]					0.7[a]
7–12 months									5[c]	60[b]					0.9[a]
1–3 years	2.5[a]	3[a]				65[a]		1[c]	7[c]	90[b]	0.2[c]	2[c]	0.3[c]		1.3[a]
4–8 years	2.5[a]	3[a]				110[a]		3[c]	12[c]	150[b]	0.3[c]	3[c]	0.6[c]		2.2[a]
9–13 years	2.5[a]	4[a]				350[a]		5[c]	23[c]	280[b]	0.6[c]	6[c]	1.1[c]		10[a]
14–18 years	2.5[a]	4[a]				350[a]		8[c]	34[c]	400[b]	0.9[c]	9[c]	1.7[c]		10[a]
Adults															
19–30 years	2.5[a]	4[a]				350[a]		10[c]	40[c]	400[b]	1.1[c]	11[c]	2[c]		10[a]
31–50 years	2.5[a]	4[a]				350[a]		10[c]	40[c]	400[b]	1.1[c]	11[c]	2[c]		10[a]
51+ years	2.5[a]	4[a]				350[a]		10[c]	40[c]	400[b]	1.1[c]	11[c]	2[c]		10[a]
>70 years	2.5[a]	4[a]				350[a]		10[c]	40[c]	400[b]	1.1[c]	11[c]	2[c]		10[a]
Pregnancy															
≥18 years	2.5[a]	3.5[a]				350[a]		8[c]	40[c]	400[b]	.9[c]	9[c]	1.7[c]		10[a]
19–30 years	2.5[a]	3.5[a]				350[a]		8[c]	40[c]	400[b]	1.1[c]	11[c]	2[c]		10[a]
31–50 years	2.5[a]	3.5[a]				350[a]		8[c]	40[c]	400[b]	1.1[c]	11[c]	2[c]		10[a]
Lactation															
≥18 years	2.5[a]	4[a]				350[a]		8[c]	34[c]	400[b]	.9[c]	9[c]	1.7[c]		10[a]
19–30 years	2.5[a]	4[a]				350[a]		10[c]	40[c]	400[b]	1.1[c]	11[c]	2[c]		10[a]
31–50 years	2.5[a]	4[a]				350[a]		10[c]	40[c]	400[b]	1.1[c]	11[c]	2[c]		10[a]

[a]Food and Nutrition Board (1997).
[b]Food and Nutrition Board (2000).
[c]Food and Nutrition Board (2001).

selenium in serum/plasma have inferential value for assessing status only to the extent that those values correlate with the sizes/activities of other physiologically relevant pools. For elements that are not highly regulated in the blood, such as zinc, that parameter has limited, if any, value in assessing status in all except severely deficient individuals.

For mineral elements such as selenium, iodine, zinc, and copper, which exert their physiological functions as essential constituents of macromolecules, assessment of status calls for measurement of the levels/activities of their respective functional forms or metabolite profiles. Thus, zinc adequacy can be determined on the basis of the cytosolic superoxide dismutase, and iodine adequacy can be determined on the basis of circulating levels of triiodothyronine (T_3), thyroid hormone (T_4), and thyroid-stimulating hormone (TSH). Similarly, plasma selenium, because it consists of several components including nonfunctional selenium bound nonspecifically in albumin and other proteins, is best assessed in cases of subadequacy by determining the selenoproteins—extracellular glutathione peroxidase and selenoprotein P.

VII. ECOLOGICAL ASPECTS OF MINERAL NUTRITION

Because the mineral elements are ultimately derived from soils, the mineral status of humans and other animals depends on the minerals available in the soils

TABLE VIII. Clinical Assessment of Mineral Element Status

	Most useful parameters of status, by general type			
Element	*Elemental analysis*[a]	*Indicator enzymes/proteins*	*Indicator metabolites*	*Physiological indices*
Ca	Serum total Ca–AAS[b], ES[c], MS[d], NAA[e], ICP-MS[f] Serum Ca^{++} – EC[g]			
P	Serum P–AAS, C[h], EC, ES, MS, GFAAS, NAA			
Mg	Serum/plasma Mg—AAS, MS, ICP-MS, NAA Serum Mg^{++}– EC Muscle Mg—AAS, MS, ICP-MS Erythrocyte Mg—AAS, MS, ICP-MS			
Na	Serum/plasma Na—Aas, C, EC, NAA Urinary Na—AAS, C, EC, NAA			
K	Serum/plasma K—AAS, C, EC, NAA Urinary K—AAS, C, EC, NAA			
Cl	Serum/plasma Cl—C, EC, NAA Urinary Cl—C, EC, NAA			
Fe	Serum Fe—AAS, GFAAS, C, EC, ES, MS, NAA, PIXE[i]	Erythrocyte hemoglobin Serum ferritin Serum transferrin Serum transferrin receptor	Free erythrocyte protoporphyrin Zn-protoporphyrin	Hematocrit Serum total Fe-binding capacity
Zn	Serum/plasma Zn—AAS, GFAAS, ES, MS Hair/nail Zn—AAS, GFAAS, ES, MS Urinary Zn–AAS, GFAAS, ES, MS Leukocyte Zn—AAS, GFAAS, ES, MS	Metallothionine I Alkaline phosphatase Carbonic anhydrase Nucleoside phosphorylase Ribonuclease		
Cu	Serum/plasma Cu—AAS, GFAAS, ES, MS, PIXE	Ceruloplasmin activity Superoxide dismutase activity Cytochrome *c* oxidase activity		
Se	Serum/plasma Zn—GFAAS, HGAAS[j] Hair/nail Se—EAAS	Glutathione peroxidase isoforms Serum selenoprotein P		
I	Urinary I—C, POT[k], NAA		Tetraiodothyronine (T_4) Thyroid hormone (T_3) Thyroid-stimulating hormone (TSH)	
Mn	Serum/plasma Mn—AAS, GFAAS, ES, MS, NAA			
Mo	Serum/plasma Mo—GFAAS, MS, NAA			
Cr	Serum/plasma Cr—GFAAS, NAA			
F	Serum/plasma F—NAA			

[a]Acceptable analytical method (typically yields CV < 10%).
[b]AAS = atomic absorption spectrophotometry.
[c]ES = emission spectroscopy.
[d]MS = mass spectrometry.
[e]NAA = neutron activation analysis.
[f]GFAAS = AAS with electrothermal atomization using a graphite furnace.
[g]EC = electrochemistry.
[h]Chemical methods.
[i]PIXE = proton-induced x-ray emission.
[j]HGAAS = hydride generation AAS.
[k]POT = potentiometry.

TABLE IX. Reference Values for Key Clinical Parameters of Mineral Element Status

Element	*Parameter*	*Reference value*[a]
Ca	Serum total Ca	86–102 $\mu g L^{-1}$
	Serum Ca^{++}	46.4–52.8 $\mu g L^{-1}$
P	Serum P	Adult: 25–45 $\mu g L^{-1}$
		Children: 40–70 $\mu g L^{-1}$
Mg	Serum/plasma Mg	16–26 $\mu g L^{-1}$
Na	Serum/plasma Na	300–350 $\mu g L^{-1}$
	Urinary Na	1950–3400 mg/d
K	Serum/plasma K	130–200 $\mu g L^{-1}$
	Urinary K	90–450 mg/d
Cl	Serum/plasma Cl	350–400 $\mu g L^{-1}$
	Urinary Cl	>40 mg L
Fe	Serum Fe	Women: 500–1700 $\mu g L^{-1}$
	Serum total Fe-binding capacity	Men: 650–1650 $\mu g L^{-1}$
		2500–4250 $\mu g L^{-1}$
	Serum ferritin	Women: 100–1200 $\mu g L^{-1}$
		Men: 200–2500 $\mu g L^{-1}$
Zn	NA[b]	plasma Zn normal range: 700–1500 $\mu g L^{-1}$
Cu	Serum/plasma Cu	Women: 800–1900 $\mu g L^{-1}$
		Pregnant women: 1180–3020 $\mu g L^{-1}$
		Men: 700–1400 $\mu g L^{-1}$
		Infants: 200–700 $\mu g L^{-1}$
		Children (6–12 y) 80–190 $\mu g L^{-1}$
Se	Plasma/serum Se	800–2000 $\mu g L^{-1}$
I	Urinary I	>1000 $\mu g L^{-1}$.
	Serum T_4	60–100 $\mu g L^{-1}$
	Serum TSH	1–50 $\mu g L^{-1}$
Mn	NA[b]	Serum/plasma Mn normal range: 4–11 $\mu g L^{-1}$
		Whole blood Mn normal range: 77–121 $\mu g L^{-1}$
Mo	NA[b]	Serum/plasma Mo normal range: 1–30 $\mu g L^{-1}$
		Whole blood Mo normal range: 8–33 $\mu g L^{-1}$
		Urine Mo normal range: 80–340 $\mu g L^{-1}$
Cr	Serum/plasma Cr	1–1.6 $\mu g L^{-1}$
F	NA[b]	NA[b]

[a]Normal range for healthy adults, unless otherwise indicated.
[b]Validated method not available.

upon which their foods were grown and through which their drinking and cooking waters drained (see Table III). Therefore, it is not surprising that mineral nutritional status can vary geographically, particularly in cases where the soil-water-plant-animal linkages are fairly direct as in the cases of grazing animals and people in highly localized food systems. Such cases have been described for iodine, copper, zinc, selenium, molybdenum, manganese, iron, boron, and cobalt (see Table X). Soil mineral deficiencies can involve intrinsically low mineral contents of soils (e.g., selenium), inefficient uptake by crops (e.g., zinc deficiency in calcareous soils), and excessive leaching (e.g., iodine, zinc). In at least two general cases, Keshan disease and the iodine deficiency diseases goiter and myxedematous cretinism, endemic distributions of a disease are directly related to the geographic patterns of soil deficiencies in selenium and iodine, respectively. Interregional and international transshipment of foods can be expected to mitigate against such local soil effects, particularly in industrialized countries (see also Chapter 15, this volume).

VIII. SUMMARY

Minerals play essential roles in the normal metabolism and physiological functions of animals and humans. Some (calcium, phosphorus, magnesium, fluoride) are required for structural functions in bone and membranes. Some (sodium, potassium, chloride) are required for the maintenance of water and electrolyte balance in cells. Some (zinc, copper, selenium, manganese, molybdenum) are essential constituents of enzymes or serve as carriers (iron) for ligands essential in metabolism. Some serve as essential components of a hormone (iodine) or hormone-like factor (chromium).

Unlike other essential nutrients, the mineral elements cannot be derived from the biosynthesis of food plants or animals—they must be obtained from soils and pass through food systems to humans in food forms. For this reason, local deficiencies of minerals in soils can produce deficiencies in local food systems which clinically impact the people dependent on those systems. The development of international trade and interregional transportation of foods has ameliorated the impact of such local mineral deficiencies. However, cases still occur in areas where the transshipment of food and, thus, the diversity of the diet are limited.

TABLE X. Examples of Geographic Patterns of Deficiencies of Nutritionally Important Mineral Elements

Element	*Known deficient areas*
I	A wide range of soils in areas remote from sea coasts; in the United States, the northwestern mountains and upper Midwest lake areas
Cu	Acid histosols in the eastern United States; acid sands in Florida; podzolic soils in Wisconsin; some sandy alkaline soils
Zn	An estimated half of the world's soils with small deficient spots in many areas; most likely in calcareous or leached, acid, sandy soils
Se	Mountainous belt of northeast China to the Tibetan plateau; parts of Africa; Pacific Northwest, northeast, and lower eastern seaboard of the United States
Mo	Acid soils; eastern seaboard, Great Lakes, and Pacific Coast areas of the United States
Mn	Humid, organic soils of the eastern United States
Fe	Seldom a problem for food plants except in arid regions
B	much of the United States, particularly in neutral-to-alkaline soils
Co	In the United States, lower Atlantic coastal plain and lower Maine coast; parts of Australia

SEE ALSO THE FOLLOWING CHAPTERS

Chapter 2 (Natural Distribution and Abundance of Elements) · Chapter 5 (Uptake of Elements from a Biological Point of View) · Chapter 8 (Biological Responses of Elements) · Chapter 15 (Selenium Deficiency and Toxicity in the Environment) · Chapter 16 (Soils and Iodine Deficiency) · Chapter 25 (Speciation of Trace Elements) · Chapter 28 (Mineralogy of Bones)

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