Boron, Manganese, Molybdenum, Nickel, Silicon and Vanadium

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I. INTRODUCTION

Elements assigned to this chapter are those whose nutritional importance is apparently limited, has not been definitively established, or is speculative. If the lack of an element cannot be shown to cause death or interrupt the life cycle (interfere with growth, development, or maturation such that procreation is prevented), many scientists do not consider that element to be essential unless it has a defined biochemical function. On this basis, of the elements assigned to this chapter, only manganese and molybdenum are unquestionably accepted as essential; they are known enzyme cofactors. Boron probably should also be considered essential because its dietary lack has been shown to interrupt the life cycle of some vertebrates. Substantial circumstantial evidence indicates that nickel, silicon and vanadium may be essential. This evidence includes:

- The element fills a need at physiological concentrations for a known in vivo biochemical action to proceed in vitro.
- The element is a component of known biologically important molecules in some life form.
- The element is essential for some lower form of life (i.e., plants, microorganisms and invertebrates).
- A dietary deprivation of the element 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.
Based on this evidence, if nickel, silicon and vanadium are not categorized as essential, they should be at least considered bioactive elements that may be nutritionally important and categorized as nutritionally beneficial, or beneficially bioactive, elements.

Although the elements in this chapter receive minimal attention in human nutrition because dietary deficiencies have not been identified in the general population, they have received some attention from individuals pursuing optimal performance and health in athletic endeavors. This attention usually has come about through the promotion of the element by the nutritional supplement industry. This promotion usually is based on some promising physiological or clinical finding, most often in an animal model or a special human situation. Too often, the findings are overstated or excessively extrapolated regarding what the element will do for the normal healthy sports enthusiast. The consumption of a diet containing all food groups most likely will provide the amounts of boron, manganese, molybdenum, nickel, silicon and vanadium needed for optimal performance of the functions that are the bases for these elements’ being of sports nutrition interest. These functions include anabolic actions through facilitating the activity of hormones such as anabolic steroids (boron) and insulin (boron, manganese and vanadium); improving bone strength and joint health (silicon, boron, manganese, nickel and vanadium); and overcoming oxidant stress induced by vigorous exercise (boron, manganese and molybdenum).

II. BORON

A. General Properties and Possible Metabolic Functions

Boron is widely distributed in nature and always bound to oxygen. Boron biochemistry is essentially that of boric acid. Dilute aqueous boric acid solutions comprise B(OH)$_3$ and B(OH)$_4$ at the pH of blood (7.4); because the pH of boric acid is 9.15, the abundance of these two species at pH 7.4 is 98.4% and 1.6%, respectively. Boric acid forms ester complexes with hydroxyl groups of organic compounds, preferably when the hydroxyl groups are adjacent and cis. Among the many substances of biological interest with which boron forms complexes are diadenosine polyphosphates, S-adenosylmethionine, pyridoxine, riboflavin, dehydroascobic acid and pyridine nucleotides. Formation of these complexes may be biologically important because some may modulate or regulate some function or reaction. To date, several naturally occurring organoboron compounds have been identified; all of these are boroesters. These compounds include antibiotics produced by microorganisms, the plant cell wall component, rhamnogalacturonan-II, and a bacterial extracellular signaling molecule.

A defined metabolic function has not been identified for boron. However, findings from boron-deprivation experiments focused on establishing essentiality provide some idea of the probable metabolic function of boron. Boron-deprivation (0.6 B μg/kg diet instead of the usual 310 mg B/kg and placed in culture water containing 0.6 μg B/L instead of the usual 100 μg B/L) in the African clawed frog (Xenopus laevis) results in necrotic eggs and a high frequency of abnormal gastrulation in the embryo. Abnormal gastrulation was characterized by bleeding yolk and exogastrulation, which suggested abnormal cell membrane structure or function. Boron deprivation of zebrafish resulted in a high rate of death during the zygote and cleavage periods before the formation of a blastula. Pathological changes in the embryo before death included extensive blebbing and the extrusion of cytoplasm, which suggested membrane alterations.

Experiments with mammals, unlike with the frog and zebrafish, have not shown that the life cycle can be interrupted. However, substantial evidence exists for boron's being a bioactive food component that is beneficial, if not required, for bone growth and maintenance, energy and reactive oxygen metabolism and optimal response to steroid hormones and insulin. Evidence that boron affects these processes in humans has come mainly from two studies in which men over the age of 45 years, postmenopausal women and postmenopausal women on estrogen were fed a diet low in boron (about 0.25 mg/200 kcal) for 63 days and then were fed the same diet supplemented with 3 mg of boron/day for 49 days. These dietary intakes were near the low and high values in the range of dietary boron
TABLE 20.1
Responses of Boron-Deprived Subjects to a 3-mg B/Day Supplement for 49 Days*

<table>
<thead>
<tr>
<th>Metabolism Affected</th>
<th>Evidence for Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macro mineral</td>
<td>Increased serum 25-hydroxyvitamin D</td>
</tr>
<tr>
<td></td>
<td>Decreased serum calcitonin†</td>
</tr>
<tr>
<td></td>
<td>Decreased serum glucose‡</td>
</tr>
<tr>
<td>Energy</td>
<td>Increased serum triacylglycerol‡</td>
</tr>
<tr>
<td></td>
<td>Decreased blood urea nitrogen</td>
</tr>
<tr>
<td></td>
<td>Decreased serum creatinine</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>Increased erythrocyte superoxide dismutase</td>
</tr>
<tr>
<td>Oxidative</td>
<td>Increased serum ceruloplasmin</td>
</tr>
<tr>
<td>Erythropoiesis/hematopoiesis</td>
<td>Increased blood hemoglobin‡</td>
</tr>
<tr>
<td></td>
<td>Increased mean corpuscular hemoglobin content‡</td>
</tr>
<tr>
<td></td>
<td>Decreased hemocrit‡</td>
</tr>
<tr>
<td></td>
<td>Decreased platelet number‡</td>
</tr>
<tr>
<td></td>
<td>Decreased red cell number‡</td>
</tr>
</tbody>
</table>

*After deprivation at an intake of 0.25 mg B/2000 kcal for 63 days. Subjects included men over the age of 45 years, postmenopausal women and postmenopausal women on estrogen therapy.
†Found when dietary copper and magnesium were inadequate.
‡Found when dietary copper and magnesium were adequate.

intakes (0.5 to 3.1mg/day) that have been found in a limited number of surveys. Some of the effects of boron supplementation after 63 days of boron depletion that were found in these two experiments are listed in Table 20.1. In one experiment, copper was marginal and magnesium was inadequate; in the other experiment, both elements were adequate. The intakes of copper and magnesium apparently affected the response to the changes in dietary boron, as indicated by the footnotes in Table 20.1. Processes affected by dietary boron in humans have been shown to also be affected in animal models.

Two hypotheses have been advanced for the biochemical function of boron in higher animals. These hypotheses accommodate a large and varied response to boron deprivation and the known biochemistry of boron. One hypothesis is that boron has a role in cell membrane function or stability such that it influences the cell response to hormones, transmembrane signaling, or transmembrane movement of regulatory cations or anions. The hypothesis is supported by the recent identification of a bacterial quorum-sensing signal molecule that is a furanosyl borate diester. Quorum sensing is the cell-to-cell communication in bacteria that is accomplished through the exchange of extracellular signaling molecules called autoinducers. The boron autoinducer (AI-2) has been proposed to be a universal signal for inter-species communication among bacteria. AI-2 is synthesized from adenosylmethionine, which supplies the 2'-3'-cis-diol of a ribose moiety that binds boron well. Another group of biomolecules that contain ribose moieties, the diadenosine phosphates, have been characterized as novel boron binders. Diadenosine phosphates function as signal nucleotides. Another study supporting the membrane role for boron was that determining the effect of boron on frog egg development. Culturing stage 1 and stage 2 oocytes from boron-adequate frogs in medium containing progesterone resulted in successful maturation to stage 5 or 6 oocytes. In contrast, oocytes from boron-deprived frogs did not respond to progesterone and did not mature in vitro. Further study of the maturation process revealed that the boron-deprived oocytes were capable of producing progesterone and the maturation-promoting factor (involved in binding progesterone to its receptor on the plasma membrane) and responding to this factor. It was hypothesized that the impaired maturation process was caused by progesterone's not being bound efficiently to the membrane receptor because of changes in its structural homology.
The second hypothesized function of boron is based on the knowledge that two classes of enzymes (oxidoreductases and hydrolases) are competitively inhibited in vitro by borate or its derivatives, and upon findings showing that dietary boron can alter the in vivo activity of many of these enzymes. Thus, it has been hypothesized that boron is a metabolic regulator; that is, boron controls a number of metabolic pathways by competitively inhibiting some key enzyme reactions. For example, reactions inhibited may include oxidoreductases that require the boron-binding cis-hydroxyl-containing pyridine of flavin nucleotides as a cofactor.

B. Basis for Sports Nutrition Interest

1. Anabolic Hormone Action Enhancement

Dietary boron may affect testosterone metabolism. A boron supplement of 3 mg/day given to postmenopausal women who had consumed a diet providing only about 0.25 mg B/day for 119 days significantly increased serum testosterone concentrations. In another study, free-living male subjects supplemented with 10 mg B/day for 4 weeks showed significantly increased plasma estradiol concentrations and a trend toward increased plasma testosterone concentrations. Rats fed a diet containing 10 mg B/kg dosed with 2 mg B/day in the drinking water showed significantly increased plasma testosterone concentrations that were diminished by doses of 12.5 and 25 mg B/day. Boron also may affect insulin production or activity. Boron deprivation increased plasma insulin concentrations in rats. Also, peak insulin secretion was higher from the pancreas isolated from boron-deprived than-supplemented chicks. These findings suggest that boron deficiency may decrease insulin sensitivity.

2. Energy Metabolism Modification

Boron status apparently has an impact on energy metabolism during exercise training. Sedentary rats responded differently to changes in dietary boron than rats exercised on a powered running wheel. Exercise-trained rats, but not sedentary rats, had higher body weights, serum lactate dehydrogenase activity, and serum creatinine concentrations when fed supplemental boron (2.0 mg B/kg diet) than when fed a low-boron diet (0.2 mg B/kg). In humans not involved in exercise training, blood urea nitrogen and creatinine concentrations were higher during boron depletion than during boron repletion. Boron deprivation increased serum glucose and decreased serum triglyceride concentrations. Dietary boron may affect glycolysis. In chicks, boron deprivation decreased the hepatic concentrations of fructose-1,6-biphosphate, glycerate-2-phosphate and dihydroxyacetone phosphate and exacerbated the cholecalciferol deficiency-induced elevation in plasma glucose and decrease in serum triglycerides. These findings suggest that the utilization of energy from carbohydrate for exercise and the body's intermediary metabolism response to exercise training are changed by boron deprivation.

3. Anti-Oxidant and Anti-Inflammatory Activity

Among the findings indicating that boron is involved in the inflammatory process or immune function in higher animals is that dietary boron affects the response to an antigen injected to induce arthritis in rats. Boron-supplemented (2.0 mg/kg diet) rats had less swelling of the paws, lower circulating neutrophil concentrations and higher circulating concentrations of natural killer cells and CD8a+/CD4- cells than did boron-deficient rats (0.1 mg/kg diet). In pigs, low dietary boron increased inflammation caused by the intradermal injection of phytohemagglutinin.

Boron may be important in the oxidative metabolite scavenging process. Boron supplementation after boron deprivation for 119 days increased erythrocyte superoxide dismutase concentrations in men and postmenopausal women. In rats, boron deprivation increased red blood cell catalase activity. These enzymes increase during increased oxidative metabolism. Evidence that boron deprivation may result in increased oxidative stress is that plasma 8-iso-prostaglandin F₂α (an indicator
of lipid oxidation) was found to be increased in boron-deprived rats. Perhaps boron regulates the inflammatory process by dampening the activity of NADP-requiring oxidoreductase, which is involved in the generation of reactive oxygen species during the respiratory burst in cells. Boron supplementation of rats attenuated hepatic pathology of rats treated with thioacetamide. Reactive oxygen metabolism is thought to be involved in the pathogenesis caused by thioacetamide.

4. Bone and Joint Health Promotion

Much evidence exists to support the contention that boron has beneficial effects on bone. The effects of boron often are most marked in the presence of suboptimal status of another nutrient important in bone formation or remodeling. One of the first studies suggesting that boron is essential found that boron improved bone calcification in chicks fed a diet deficient but not completely lacking in vitamin D. At the microscopic level, boron deprivation (0.465 mg/kg diet) exacerbated the distortion of marrow sprouts (location of calcified scaffold erosion and new bone formation) and the delay in initiation of cartilage calcification in bones during marginal vitamin D deficiency. Boron deprivation also decreased chondrocyte density in the zone of proliferation of the bone growth plate. It should be noted that vitamin D-deficient chicks fed low dietary boron (about 0.3 mg/kg), compared with chicks fed diets containing 1.4 mg B/kg, had decreased plasma 25-hydroxycholecalciferol. In humans, estrogen therapy to maintain bones increases serum 17β-estradiol; this increase is depressed when dietary boron intake is low (0.25–0.35 mg/day). In rats, boron enhanced the beneficial effects of 17β-estradiol on trabecular bone volume and plate density in tibias of ovariectomized rats. Although neither boron or estradiol supplementation alone affected calcium, phosphorus or magnesium balance, a combined boron and estradiol supplementation improved the apparent absorption (based on the analysis of food, urine and feces) of calcium, magnesium and phosphorus and retention and serum concentrations of calcium and magnesium in ovariectomized rats. Boron deprivation also can exacerbate the increase in serum calcitonin caused by low dietary copper and magnesium in humans. Boron deprivation without modification by other nutrients affects bone strength. Low dietary boron (0.98 mg boron/kg compared with 5 mg boron/kg) decreased the bone strength variable bending moment in pigs and induced abnormal limb development in frogs (boron low conditions described in section A). In rats, boron deprivation decreased femur strength measured by the breaking variables bending moment and stress.

Supra nutritional or pharmacologic doses of boron also may be beneficial to bone mechanical properties. A boron supplement of 5 mg/kg to a diet containing 9.4 mg B/kg increased bone strength in chicken. Also, chicks fed a diet containing 14.7 mg B/kg and supplemented with 50 or 100 mg B/kg for 16 weeks after hatching had increased bone strength as indicated by increased shear force of the tibia and femur, shear stress of the tibia and shear energy of the femur. When the boron supplements were started at 32 weeks of age and fed for 40 weeks, the shear fracture energy of both the tibia and radius was increased in egg producing chickens and the shear force, stress and fracture energy of both the tibia and radius were increased in non-egg-producing chickens. Supplementing a standard diet with 35 (and up to 1575) mg B/kg as boric acid increased vertebral resistance to a crushing force by approximately 10% in rats.

In rats exposed to strenuous treadmill exercise, femur and vertebra bone mineral content and density were decreased and trabecular separation was increased. A boron supplement of 50 mg/kg as sodium borate increased bone mineral content and density, trabecular bone volume and trabecular thickness in the exercised rats. It was concluded that boron preserves bone mass in rats that have been exposed to intense exercise.

C. Metabolism

Because there is no usable radioisotope of boron, the study of its metabolism has been difficult. It is likely, however, that most ingested boron is converted into boric acid, the normal hydrolysis end
product of most boron compounds and the dominant inorganic species at the pH of the gastrointestinal tract. About 85% of ingested boron is absorbed and then efficiently excreted via the urine mainly as boric acid.\(^{41-43}\) During transport in the body, boric acid most likely is weakly attached to organic molecules containing cis-hydroxyl groups.

### D. Dietary and Supplemental Sources

The richest sources of boron are fruits, vegetables, pulses, legumes and nuts.\(^{44-48}\) Wine, cider and beer are also high in boron. Dairy products, fish, meats and most grains are poor sources of boron, although milk is the primary source of boron for infants, toddlers and adolescents because of the large quantities consumed. A typical daily intake of boron through diet ranges between 0.75 and 1.35 mg. However, consumption of specific foods with a high boron content will increase boron intake significantly; for example, one serving of wine or avocado provides 0.4 and 1.11 mg., respectively.

### E. Supplementation

Within 3 months of the first report describing findings from nutritional experiments with humans,\(^{45}\) boron supplements were being marketed. Shortly thereafter, numerous health claims for boron began to appear in tabloids, magazines, advertisements and other popular media. The claims included boron’s preventing or curing osteoporosis, being an ergogenic aid, preventing or curing arthritis, stopping memory loss and keeping motor skills sharp.

No reports show that boron supplementation of athletes has significant beneficial effects on performance. One report described findings from a study in which athletic and sedentary women consuming self-selected Western diets were supplemented with 3 mg of boron for 10 months.\(^{48}\) This report did not indicate that boron affected physical work capacity, but did present some findings suggesting that exercise modifies the effect of boron supplementation on mineral status. The boron supplementation decreased serum phosphorus concentrations; this effect was diminished by exercise training. Also, boron supplementation increased serum magnesium concentrations in sedentary women but not in athletes. In another study, 10 male bodybuilders consumed a daily 2.5-mg boron supplement while nine bodybuilders consumed a placebo daily for 49 days.\(^{49}\) Seven weeks of bodybuilding increased total testosterone, lean body mass and strength in lesser-trained bodybuilders; these effects were not significantly altered by the boron supplementation.

Boron is not very toxic when orally ingested.\(^{50}\) Evidence for this low toxicity includes the use of boric acid and borates as food preservatives and in oral medicinal products in the late 19th and early 20th centuries. Toxicity signs in animals generally occur only after dietary boron exceeds 100 mg/kg diet. In humans, the signs of acute toxicity include nausea, vomiting, diarrhea, dermatitis and lethargy. The signs of chronic toxicity, based mainly on animal findings, include poor appetite, weight loss and decreased sexual activity, seminal volume and sperm count and motility.

### F. Dietary Recommendations

In the human studies described above, the subjects responded to boron supplementation (3 mg/day) after consuming a diet supplying only about 0.25 mg of boron/2000 kcal for 63 days. Thus, humans apparently receive benefit from a boron intake above 0.25 mg per day or have a dietary boron requirement above this amount. A World Health Organization Expert Consultation on Trace Elements in Human Nutrition suggested that an acceptable safe range of population mean intakes for boron for adults could be 1 to 13 mg per day.\(^{11}\) The U.S. FNB (FNB) chose not to establish recommendations for daily boron intake because of the lack of a clear biological function for boron in humans and the limited evidence on which to base a recommendation. The FNB did, however, set tolerable upper intake levels (UL) for different age groups for boron.\(^{51}\) The ULs are based largely
on adverse reproductive and developmental effects in animals as the critical endpoint. The UL for adults is 20 mg/day.

G. FUTURE RESEARCH DIRECTIONS OR NEEDS

Numerous findings suggest that boron status could affect body processes of interest in sports nutrition. However, the possibility that boron status can affect athletic performance has not been adequately investigated. Studies are needed to determine whether boron supplementation can improve performance of athletes regularly consuming low amounts of boron (<1.0 mg/day). These studies would be helped by the establishment of a defined biochemical function and a reliable status indicator for boron. Also, studies are needed to determine whether supra nutritional intakes, but below the UL guideline of 20 mg B/day, provide benefits to athletes. Until such studies are done, no firm conclusions can be made about the value of increased boron intakes in sports nutrition.

III. MANGANESE

A. GENERAL PROPERTIES AND METABOLIC FUNCTIONS

The essentiality of manganese for animals has been known for more than 50 years; its deficiency has been induced in many animal species. 52 Deficiency causes depressed growth, testicular degeneration (rats), slipped tendons or perosis (chicks), osteodystrophy, severe glucose intolerance (guinea pigs), ataxia (mice, mink), depigmentation of hair, and seizures (rats). Manganese deficiency also caused defects in lipid and carbohydrate metabolism.

Signs of manganese deficiency in humans have not been firmly established. Most reports of human manganese deficiency have shortcomings. In one study, 52 men were fed a purified diet supplying only 0.11 mg Mn/day for 39 days. The men developed a finely scaling, minimally erythematous rash, decreased serum cholesterol concentrations and increased serum alkaline phosphatase activity. Short-term (10 days) manganese supplementation, however, did not reverse these changes. In another study, 14 young women were fed a conventional Western-type diet providing about 1.0 mg Mn/day for 39 days and then compared with when the diet was supplemented with manganese to provide about 5.6 mg/day. 53 The low manganese intake resulted in slightly increased plasma glucose concentrations during an intravenous glucose tolerance test and increased menstrual losses of manganese, calcium, iron and total hemoglobin. These findings need to be confirmed because the women did not exhibit negative manganese balance during the low manganese period, nor were the changes very marked. The most convincing case of manganese deficiency is that of a child on long-term parenteral nutrition who exhibited diffuse bone demineralization and poor growth that were corrected by manganese supplementation. 54,55

Manganese deficiency may contribute to disease processes. Low dietary manganese or low blood and tissue manganese has been associated with osteoporosis, diabetes, epilepsy, atherosclerosis, impaired wound healing and cataracts. 56

Because manganese deficiency has been so difficult to induce or identify in humans, it generally is considered not of nutritional concern. Nonetheless, manganese is considered an essential nutrient for humans because it is known to function as an enzyme activator and to be a constituent of several metalloenzymes. 57 The numerous enzymes that can be activated by manganese include oxidoreductases, lyases, ligases, hydrolases, kinases, dehydrogenases and transferases. Most enzymes activated by manganese in higher animals and humans can also be activated by other metals, especially magnesium: exceptions are the manganese-specific activation of glycosyltransferases, glutamine synthetase, farnesy] pyrophosphate synthetase and phosphoenolpyruvate carboxykinase. 57 The few manganese metalloenzymes include arginase, pyruvate carboxylase and manganese superoxide dismutase in higher animals. 57
B. BASIS FOR SPORTS NUTRITION INTEREST

1. Energy Metabolism Modification

Pyruvate carboxylase and phosphoenolpyruvate carboxykinase are important enzymes in the gluconeogenic pathway. Because pyruvate carboxylase is a manganese metalloenzyme and phosphoenolpyruvate carboxykinase is a manganese-activated enzyme, it can be predicted that manganese deficiency affects carbohydrate metabolism through changing the activity of these enzymes in liver. However, even in severely manganese-deficient animals, pyruvate carboxylase activity is not affected. Manganese deficiency inconsistently affects phosphoenolpyruvate carboxykinase activity.

Manganese apparently affects carbohydrate metabolism through an effect on insulin production, secretion or degradation. Offspring of manganese-deficient guinea pig dams that were weaned to manganese-deficient diets exhibited impaired glucose tolerance and glucose utilization. Insulin release from isolated perfused pancreas from manganese-deficient rats is less than that found with manganese adequacy. Increased insulin degradation was also found in rats. In both the guinea pig and rat, manganese deficiency causes pancreatic pathology characterized by hypoplasia of all cellular components. Decreased preproinsulin mRNA may be contributing to decreased insulinogenesis in the manganese-deficient rat. Manganese deficiency also apparently causes a defect in the response to insulin in peripheral tissues because adipocytes isolated from manganese-deficient rats had decreased in vitro insulin-stimulated glucose transport, oxidation and conversion to fatty acids. The biochemical bases for the changes in insulin metabolism and action induced by manganese deficiency have not been clearly defined.

2. Anti-Oxidant Activity

Manganese superoxide dismutase is the major antioxidant in mitochondria. The importance of this enzyme was demonstrated by the finding that the deletion mutation of the manganese superoxide dismutase gene in mice resulted in death within 5–21 days of birth. Severe mitochondrial damage occurred in these rats that was attributed to the increased presence of reactive oxygen species. The importance of this enzyme for protection against oxidant stress has also been demonstrated by studies with animals or cells that overexpress manganese superoxide dismutase. For example, this overexpression has been shown to prevent alcohol-induced liver injury in rats, attenuate myocardial injury following ischemia and reperfusion, protect lung epithelial cells against oxidant injury and protect against apoptotic cell death. In addition, high dietary manganese protected against heart lipid peroxidation in rats fed high amounts of polyunsaturated fatty acids. Physiological stress, including exercise, increases the activity of manganese superoxide dismutase in the myocardium and thus apparently protects against ischemia-perfusion-induced arrhythmias, myocardial stunning and infarction. These findings indicate that manganese is important for protection against oxidant damage induced by high-intensity training and promotes recovery from training.

3. Bone and Joint Health Promotion

When imposed in utero or in young growing animals, manganese deficiency has marked adverse effects on the skeleton; these effects include shortening of the limbs, enlargement of the joints, twisting of legs, stiffness and lameness. These skeletal abnormalities have been largely ascribed to a reduction in proteoglycan synthesis secondary to a reduction in the activities of manganese-dependent glycosyl transferases. However, manganese deficiency also has been found to impair osteoblast and osteoclast activities. This impairment may lead to altered bone growth and remodeling that contribute to bone deformities. Also, manganese deficiency decreases circulating insulin-like growth factor, which has osteotropic actions. This may be the reason that manganese deficiency decreased bone density and calcium in rats. The preceding findings suggest that manganese may be important in maintaining strong bones and healthy joints in physically active people.
C. Metabolism

For the adult human, absorption of manganese from the diet has often been stated to be no higher than 5%. This estimate is complicated by the fact that endogenous manganese is almost totally excreted through biliary, pancreatic and intestinal secretions into the gut. If manganese status is adequate, endogenous excretion of absorbed manganese into the gut is so rapid that it is difficult to determine the portion of fecal manganese not absorbed from the diet and the portion endogenously excreted. With this in mind, true absorption of manganese has been estimated to be 8% in young rats. Manganese absorption declines as dietary intake increases and increases with low manganese status. Endogenous excretion of manganese apparently is not markedly influenced by dietary intake or status. Thus, variable absorption apparently is a significant factor in the regulation of manganese homeostasis, with excretion contributing.

Absorption of manganese apparently occurs equally well throughout the small intestine. There are indications that manganese is absorbed through a rapidly saturable, active transport mechanism that involves a high-affinity, low-capacity system. Diffusion also has been implicated in manganese absorption. Perhaps both processes are involved in manganese movement across the gut. This suggestion is supported by the finding that apical to basolateral manganese uptake and transport by Caco-2 cultures were strictly concentration-dependent, but basolateral to apical uptake and transport were saturable. Manganese may be absorbed by a 2-step mechanism with the initial uptake from the lumen followed by transfer across mucosal cells. Iron competes with manganese for common binding sites in both processes. Thus, one of these metals, if present in high amounts, can exert an inhibitory effect on the absorption of the other.

Both Mn²⁺ bound to plasma α-2-macroglobulin and Mn²⁺ bound to albumin have been suggested to be the form of manganese entering the portal blood from the gastrointestinal tract. Regardless of form, manganese is rapidly removed from the blood by the liver. A fraction is oxidized to Mn³⁺ and is transported in plasma bound to transferrin or possibly to a specific transmembrane protein. Transferrin-bound manganese is taken up by extrahepatic tissue.

Within cells, manganese is found predominantly in mitochondria, and thus, liver, kidney and pancreas have relatively high manganese concentrations. In contrast, manganese is present in extremely low concentrations in plasma and urine of humans.

D. Dietary and Supplemental Sources

Most reported daily mean intakes of manganese throughout the world fall between 0.52 and 10.8 mg. Unrefined cereals, nuts, leafy vegetables and tea are rich in manganese. These foods contributed almost 75% of the manganese consumed by the average adult human male in the Total Diet Study. Refined grains, meats and dairy products are low in manganese.

E. Supplementation

Apparently because manganese deficiency is difficult to induce or identify in humans, there is a paucity of studies determining the effect of manganese supplementation on healthy adults. Women consuming diets averaging between 1.4 and 2.0 mg/day had only increased lymphocyte manganese superoxide dismutase activity and serum manganese concentrations after receiving a supplemental 15 mg Mn/day for 124 days. In another study, healthy young women were fed 8 weeks each, in a crossover design, diets that provided 0.8 or 20 mg Mn/day. The manganese intakes did not affect any clinical or neurological measures and only minimally affected psychological variables. Based on these findings it was concluded that dietary intakes of manganese from 0.8 to 20 mg/day for 8 weeks are not likely to result in either manganese deficiency or toxicity signs in healthy adults.

In the past, manganese was considered to be one of the least toxic of the essential mineral elements. Very high amounts of manganese (2,000–7,000 mg/kg diet) were required to induce the most commonly reported signs (depressed growth and iron status and hematological changes) of
manganese toxicity in animals. Recently, however, magnetic resonance imaging has shown that signals for manganese in the brain are strongly associated with neurological symptoms (e.g., sleep disturbances) exhibited by patients with chronic liver disease. Findings such as this have resulted in the suggestion that high intakes of manganese are ill-advised because of potential neurotoxicological effects, especially in people with compromised homeostatic mechanisms or infants whose homeostatic control of manganese is not fully developed.

High intakes of manganese may be of concern for people not consuming adequate amounts of magnesium. Pigs fed diets providing inadequate magnesium (about 25% the dietary recommendation) died suddenly and showed heart changes when the diet was made rich in manganese (52 mg/kg). Neurotoxicity was the adverse effect used by the FNB to set the UL for manganese. The UL (mg/day) for children was set at 2 for ages 1–3 years, 3 for 4–8 years, 6 for 9–13 years and 9 for 14–18 years. Above the age of 19 years, the UL set was 11 mg/d.

F. Dietary Recommendations

The FNB has set Adequate Intakes (AIs) for manganese (in mg/day) as follows: infants 0–6 months, 0.003; infants 7–12 months, 0.6; children 1–3 years, 1.2; children 4–8 years, 1.5; boys 9–13 years, 1.9; boys 14–18 years, 2.2; girls 9–18 years, 1.6; adult men, 2.3; adult women, 1.8; pregnant women, 2; and lactating women, 2.6. These values seem quite liberal considering the difficulty in inducing or identifying manganese deficiency in humans. Intensive exercise may increase the need for manganese because a 30-km cross-country run has been found to increase intestinal excretion and induce negative balance.

G. Future Research Directions or Needs

Findings described above suggest that exercise may increase the need for manganese superoxide dismutase to protect against oxidative stress, and suggest that exercise may increase manganese loss. Also, low dietary manganese or low blood and tissue manganese has been associated with disturbances in carbohydrate metabolism (e.g., impaired insulin production or response to glucose, and perhaps impaired gluconeogenesis) and bone loss. Thus, there is a need to ascertain whether manganese supplementation of individuals consuming diets low in manganese and performing intensive exercise would benefit from an increased intake of manganese.

IV. MOLYBDENUM

A. General Properties and Metabolic Functions

The signs of molybdenum deficiency in animals have been reviewed. In rats and chickens, molybdenum deficiency aggravated by excessive dietary tungsten results in the depression of molybdenum enzymes, disturbances in uric acid metabolism and increased susceptibility to sulfite toxicity. In goats, deficiency uncomplicated by high dietary tungsten or copper resulted in depressed food consumption and growth, and impaired reproduction characterized by infertility and elevated mortality in both mothers and offspring.

Knowledge of the signs and symptoms of human molybdenum deficiency have come from a patient receiving prolonged total parenteral nutrition. This patient developed hypermethioninemia, hypouricemia, hyperoxypurinemia, hypouricosuria and very low sulfate excretion; these changes were exacerbated by methionine administration. The findings indicated defects in the oxidation of sulfite to sulfate and in uric acid production. Supplementation of the patient with ammonium molybdate improved the clinical condition, reversed the sulfur-handling defect and normalized uric acid production. Molybdenum deficiency has not been unequivocally identified in humans other than in this individual. Thus, molybdenum generally is considered to be of no practical nutritional concern for humans. Consequently, relatively little effort has been devoted to the study of the human nutritional and metabolic aspects of molybdenum.
Although molybdenum nutrition receives relatively little attention, it is considered an essential nutrient for all forms of life because it is a known cofactor for some enzymes. In humans, three molybdoenzymes have been identified: aldehyde oxidase, which oxidizes and detoxifies various pyrimidines, purines, pteridines and related compounds; xanthine oxidase/dehydrogenase, which catalyzes the transformation of hypoxanthine to xanthine and of xanthine to uric acid; and sulfite oxidase, which catalyzes the transformation of sulfite to sulfate. In these enzymes, molybdenum is present at the active site in a small nonprotein cofactor containing a pterin nucleus.\(^{95}\)

### B. Basis for Sports Nutrition Interest

There is relatively little reason for molybdenum to be of interest to physically active people. Molybdenum is a transition element that readily changes its oxidation state and can thus act as an electron transfer agent in oxidation-reduction reactions in which it cycles from Mo\(^{6+}\) to reduced states. This is the basis for molybdoenzymes’ catalyzing the hydroxylation of various substrates using oxygen from water. Molybdenum hydroxylases may be important in metabolizing drugs and foreign compounds that enter the body.\(^{96}\) Thus, low dietary molybdenum might be detrimental to an athlete’s health through an inability to effectively detoxify some xenobiotic compounds.

There is some limited evidence that molybdenum may have insulin mimetic effects. Feeding high amounts of molybdenum (0.5–1.0 g/L in water plus 1.5–2.0 g/kg diet) prevented fructose-induced hyperglycemia, hyperinsulinemia and hypertension and partially prevented increased plasma triglyceride concentrations in rats.\(^{97}\) Treating rats with sodium molybdate (100 mg/kg body weight per day) significantly reversed changes in carbohydrate metabolizing (both oxidation and storage) enzymes, and regulated blood sugar concentrations in rats with alloxan-induced diabetes.\(^{98}\) The doses of molybdenum used in these two studies were extremely high. The estimated dietary requirement of the rat is 150 μg Mo/kg, and 100-mg Mo/kg diet not high in sulfur apparently is toxic because it reduced growth.\(^{99}\) Thus, it would be irresponsible to suggest that ingesting supra nutritional intakes of molybdenum would result in insulin-like actions that could help athletic performance.

### C. Metabolism

Molybdenum in foods and in the form of soluble complexes is readily absorbed. Humans absorbed 88–93% of the molybdenum fed as ammonium molybdate in a liquid formula component of a diet.\(^{100}\) In another study, about 57% of intrinsically labeled molybdenum in soy and about 88% in kale was absorbed.\(^{101}\) Molybdenum absorption occurs rapidly in the stomach and throughout the small intestine, with the rate of absorption being higher in the proximal than in the distal parts. Molybdate may be transported across the gastrointestinal tract by both diffusion and active transport, but at high concentrations the relative contribution of active transport to molybdenum flux is small.\(^{102}\) The absorption and retention of molybdenum are influenced strongly by interactions between molybdenum and various dietary forms of sulfur.\(^{93}\)

Molybdate is transported loosely attached to erythrocytes in blood where it tends to bind specifically to α-2-macroglobulin.\(^{103}\) Organs that retain the highest amounts of molybdenum are liver and kidney.\(^{93,104}\) The molybdenum in liver is entirely present in macromolecular association, partly as known molybdoenzymes and the remainder as the molybdenum cofactor.\(^{95}\)

After absorption, most molybdenum is turned over rapidly and eliminated as molybdate through the kidney;\(^{100}\) this elimination is increased as dietary intake is increased. Thus, excretion rather than regulated absorption is the major homeostatic mechanism for molybdenum.

### D. Dietary and Supplemental Sources

Plant foods are the major sources of molybdenum in the diet and their molybdenum content depends on the content of the soil in which they are grown. Good food sources of molybdenum include legumes, grain products and nuts. Milk and milk products and organ meats (liver and kidney) also
are rich sources of molybdenum. Poor sources of molybdenum include nonleguminous vegetables, fruits, oils, fats and fish.\textsuperscript{102} Two studies of molybdenum intakes in the United States yielded average intakes ranging from 76–240 µg/day for adults.\textsuperscript{104,105} These intakes indicate that almost all diets should meet the recommended dietary allowance (RDA) of 45 µg/day for molybdenum.\textsuperscript{51}

E. Supplementation

Because molybdenum deficiency has not been unequivocally identified in humans other than the aforementioned individual on total parenteral nutrition, molybdenum generally is considered to be of no practical nutritional concern for humans. Consequently, relatively little effort has been expended toward studying the effect of molybdenum supplementation on health and well-being. Turnland et al.\textsuperscript{106} fed four young men five amounts of molybdenum, ranging from 22–1490 µg/day, for a period of 24 days each. No adverse effects were observed at any of the intakes. Urinary excretion of uric acid was decreased and urinary xanthine excretion was increased in response to a load dose of adenosine monophosphate when the men were adapted to the lowest molybdenum intake (22 µg/day); these findings indicate that xanthine oxidase activity was decreased by the low-molybdenum regime. In a separate study, the low-molybdenate diet was fed for 102 days; no biochemical signs of deficiency were observed.\textsuperscript{106}

Molybdenum has relatively low toxicity. Based on detrimental effects of molybdenum on reproduction and fetal development in animals, the FNB set the following ULs for molybdenum (µg/day): age 1–3 years, 300; age 4–8 years, 600; age 9–13 years, 1100; age 14–18 years, 1700; and over age 18 years, 2000.\textsuperscript{51}

F. Dietary Recommendations

The FNB set the following RDAs for molybdenum (µg/day): children 1–3 years, 17; 4–8 years, 22; 9–13 years, 34; and 14–18 years, 43. The RDA for men and women ages ≥19 years was set at 45 µg/day, except for 50 µg/day during pregnancy and lactation.\textsuperscript{51}

G. Future Research Directions or Needs

A study of male intercollegiate runners and female high-school basketball players found that a marked decrease in blood molybdenum occurred with strenuous exercise.\textsuperscript{107} It was suggested that molybdenum deficiency was caused by strenuous exercise, but no indication of decreased performance or recovery from oxidative stress was reported with this decrease in blood molybdenum. Further studies are needed to ascertain whether athletes performing strenuous physical activity and consuming low dietary molybdenum respond to molybdenum supplementation.

V. Nickel

A. General Properties and Possible Metabolic Functions

Nickel is essential for some lower forms of life where it participates in hydrolysis and redox reactions, regulates gene expression and stabilizes certain structures. In these roles, nickel forms ligands with sulfur, nitrogen and oxygen, and exists in oxidation states 3\textsuperscript{+}, 2\textsuperscript{+} and 1\textsuperscript{+}. In lower forms of life, nickel has been identified as an essential component of six different enzymes: urease, hydrogenase, carbon monoxide dehydrogenase, methyl-coenzyme M reductase, Ni-superoxide dismutase and glyoxalase I.\textsuperscript{108} Interestingly, the substrates or products for all these enzymes are dissolved gases: hydrogen, carbon monoxide, carbon dioxide, methane, oxygen and ammonia.

Nickel is generally not accepted as an essential nutrient for higher animals and humans, apparently because of the lack of a clearly defined specific biochemical function. However, nickel deprivation studies show that it has beneficial, if not essential, functions in several experimental models. Nickel deprivation detrimentally affects vision, sperm production and motility, blood pressure, iron metabolism
and sodium homeostasis in animals.\textsuperscript{109,110} Biochemical changes induced by nickel deprivation in chicks, goats, pigs and rats include altered metabolism of carbohydrates, amino acids and lipids and distribution of calcium, iron and zinc.\textsuperscript{111-113} Nickel might have a function that is associated with vitamin B\textsubscript{12} because the lack of this element inhibits the response to nickel supplementation when dietary nickel is low,\textsuperscript{114} and nickel can alleviate vitamin B\textsubscript{12} deficiency in higher animals.\textsuperscript{115}

B. Basis for Sports Nutrition Interest

1. Energy Metabolism Modification

There is considerable evidence that dietary nickel influences carbohydrate and lipid metabolism in experimental animals. Some of the first studies suggesting that nickel may be essential showed that rats fed a 0.015-mg Ni/kg diet compared with those fed a 20-mg Ni/kg diet had depressed activities of enzymes that degrade glucose to pyruvate and enzymes that produce energy through the citric acid cycle; these enzymes included glucose-6-phosphate dehydrogenase, isocitrate dehydrogenase and malate dehydrogenase.\textsuperscript{116} Also, glucose, glycogen and triglycerides were reduced in the liver, and ATP and glucose were reduced in serum of rats fed low dietary nickel.\textsuperscript{116} The amount of nickel fed to the supplemented controls was quite high relative to the suggested nickel requirement of rats of 0.15–0.2 mg/kg diet.\textsuperscript{117} Because this high dietary concentration of nickel can affect iron metabolism in an apparent pharmacologic manner,\textsuperscript{118} uncertainty existed about whether the changes in carbohydrate and lipid metabolism variables were caused by a nickel deprivation or pharmacologic action. Later studies using more nutritionally balanced diets and a lower amount of nickel supplementation showed that some of the differences were probably caused by nickel deprivation. Compared with animals fed a diet supplemented with 1 mg Ni/kg, rats fed 0.013 mg Ni/kg had decreased liver activities of the lipogenic enzymes glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, malic enzyme and fatty acid synthase.\textsuperscript{119} Nickel deprivation also caused increased concentrations of triacylglycerol concentrations in liver and serum. Other studies have indicated that about 0.03-mg compared with 1-mg Ni/kg diet resulted in increased plasma lipids.\textsuperscript{120} Because the enzymes affected by nickel deprivation are not nickel enzymes, the mechanism through which nickel affects glucose and lipid metabolism is not clear. However, because nickel apparently can affect iron metabolism through both physiologic and pharmacologic mechanisms,\textsuperscript{118,119} and iron status can affect energy metabolism, some of the changes induced by nickel deprivation may have been caused by a depressed iron status or utilization. Also, the effects of nickel deprivation might have been partly caused by a change in thyroid hormone metabolism because nickel deprivation has been shown to decrease the concentrations of circulating thyroxine, triiodothyronine and free thyroxine.\textsuperscript{121} The mechanism through which nickel affects thyroid hormone metabolism is also unknown.

Nickel supplemented in high amounts may affect glucose and lipid metabolism through affecting the action of insulin. In 1926, it was reported that nickel intensified and prolonged the hypoglycemic action of insulin administered to dogs and rabbits.\textsuperscript{122,123} About 40 years later, it was found that nickel enhanced glucose uptake, its oxidation to carbon dioxide and incorporation into fat-pad lipids in vitro, thus simulating the action of insulin.\textsuperscript{124} Nickel chloride (10 mg/kg body weight) injected before streptozotocin prevented streptozotocin-induced hyperglycemia in rats.\textsuperscript{125} Long-term high nickel ingestion (200 mg/L as NiCl\textsubscript{2} in drinking water) by rats was found to increase insulin binding by their epididymal adipocytes.\textsuperscript{126} Additionally, a decreased sensitivity to the antilipolytic response to insulin was found in adipocytes from the rats fed high nickel. This latter effect may explain why nickel-supplemented controls fed a high 20-mg Ni/kg diet had higher, while those fed a moderate 1 mg Ni/kg had lower liver triglycerides compared with rats fed about 0.015-mg Ni/kg diet (see above). That is, the high effect was pharmacologic and the moderate effect was nutritional.

The findings described above suggest that low dietary nickel impairs the activity of glucose-degrading and lipogenic enzymes and high dietary nickel can affect enhanced glucose degradation and lipid concentrations through affecting insulin action. These contrasting effects of nickel at
apparent deficient and pharmacologic intakes may explain some of the divergent results found with indicators of glucose and lipid metabolism in early nickel-deprivation studies; in these studies, supplemented controls were fed a 3- to 20-mg Ni/kg diet. Nonetheless, the findings indicate that nickel can affect energy metabolism.

2. Bone and Joint Health Promotion

There is evidence that nickel has beneficial effects on bone. Early findings suggesting such an effect include nickel deprivation increasing liver alkaline phosphatase activity in rats,\textsuperscript{127} decreasing femur calcium and phosphorus content in rats,\textsuperscript{128} and decreasing the calcium concentration in ribs, carpal bones and skeleton in miniature pigs.\textsuperscript{129} Subsequently, it was found that high dietary nickel (25-mg/kg diet) improved bone-breaking variables in male broilers.\textsuperscript{130} Nickel increased the shear fracture energy of the tibia and the shear force, stress and fracture energy of the radius. Nickel deprivation was found to decrease the bone-breaking variables maximum force and moment of inertia in rats.\textsuperscript{131} In contrast to earlier studies in which supplemented controls were fed high dietary nickel (10–20-mg/kg diet), this study (supplemented controls fed 1-mg Ni/kg diet) did not find decreased calcium and phosphorus concentrations in the tibia. The mechanisms through which nickel affects bone strength and composition have not been defined. Nickel deprivation most likely has an effect on the organic matrix of bone because nickel was incorporated mostly in the organic phase of mouse calvaria \textit{in vitro},\textsuperscript{132} and nickel can bind to cartilage oligomeric matrix protein and bring about the binding of this protein with collagen I/II and procollagen I/II.\textsuperscript{133} In high amounts, nickel may affect bone composition through activating the osteoclast calcium "receptor," which results in an increase in intracellular Ca\textsuperscript{2+}.\textsuperscript{134} This increase is a signal for the osteoclasts to resorb less bone.

C. Metabolism

It is generally accepted that less than 10% of nickel ingested with food by humans or animals is absorbed.\textsuperscript{135,136} When soluble nickel in water is ingested after an overnight fast, as much as 50%, but usually closer to 20–25% of the dose is absorbed.\textsuperscript{136–138} Nickel absorption is heightened by iron deficiency,\textsuperscript{139} pregnancy\textsuperscript{140} and lactation.\textsuperscript{141} The mechanisms involved in the transport of nickel through the gut are not conclusively established, but both active and passive processes are thought to be involved.\textsuperscript{142,143} It has been suggested that some nickel is transported through an iron-transport system,\textsuperscript{139} and cobalt can compete with these elements for transport.\textsuperscript{144} Nickel homeostasis may be partially regulated by absorption from the gut. The rate of nickel transfer was greater in everted jejunal sacs from nickel-deprived than nickel-adequate rats.\textsuperscript{145}

Nickel is transported in blood principally bound to serum albumin. Small amounts of nickel in serum are associated with the amino acids histidine and aspartic acid and with $\alpha$-2-macroglobulin (nickeloplasmin).\textsuperscript{146,147} Uptake of soluble nickel from serum into tissues is believed to be governed by ligand exchange reactions.\textsuperscript{148} It has been suggested that histidine removes nickel from serum albumin and mediates its entry into cells. The transfer of nickel across plasma membranes apparently involves both active and diffusion mechanisms, which have not been defined. Soluble nickel may share a common transport system with magnesium or iron (e.g., transported into the cell bound to transferrin) and some soluble nickel probably enters cells via calcium channels.\textsuperscript{148} Insoluble nickel compounds enter the cell via phagocytosis.\textsuperscript{148}

Although fecal nickel excretion (mostly unabsorbed nickel) is 10–100 times as great as urinary excretion, most of the small fraction of absorbed nickel is rapidly and efficiently excreted through the kidney as urinary low-molecular-weight complexes.\textsuperscript{149} In healthy humans, urinary nickel concentrations generally range from 0.1–13.3 $\mu$g/L.\textsuperscript{148} The nickel content of sweat of humans is high (about 70 $\mu$g/L), which points to active secretion of nickel by the sweat glands.\textsuperscript{150} Based on isotopic studies in which nickel was administered intravenously, excretion of exogenous nickel through the bile or gut is insignificant.\textsuperscript{151,152}
D. **Dietary and Supplemental Sources**

Rich sources of nickel include chocolate, nuts, dried beans, peas and grains. Nickel concentrations are low in meats, milk and milk products. Typical daily dietary intakes for nickel are 70–260 µg.\(^{153}\)

E. **Supplementation**

Because nickel has not been established as an essential element, and indicators of nickel status have not been identified, there has been no stimulus to determine the effect of nickel supplementation on healthy adults.

Except for the possibility that individuals with a nickel allergy may be sensitive to intakes of soluble nickel after fasting, there is no evidence that associates exposure to nickel through consumption of a normal diet with adverse effects on humans. The FNB,\(^{31}\) however, did set an UL of 0.017 mg Ni/kg body weight/day; this translates into about 1.0 mg/day of soluble nickel salts for adolescents aged 14–18 years and adults. The UL (mg/day) set for children 1–3 years was 0.2, 4–8 years was 0.3 and 9–13 years was 0.6. The basis for the UL was a NOAEL of 5 mg/kg body weight/day for rats and an uncertainty factor of 300.

F. **Dietary Recommendations**

The FNB set no RDA for nickel.\(^{31}\) However, based on animal studies, if a dietary requirement is found for humans, it most likely will be less than 100 µg/day.\(^{153}\) Exercising individuals may have a higher nickel need than sedentary individuals because aerobic exercise increases the urinary excretion of nickel.\(^{154}\)

G. **Future Research Directions or Needs**

Before any dietary or supplement recommendations can be made for physically active people, much needs to be learned about nickel. Foremost is the need to establish the biochemical functions or the mechanisms through which nickel is beneficial to carbohydrate, lipid and bone metabolism. Knowledge of these functions or mechanisms would permit the assessment of the effects of low and supra nutritional dietary intakes of nickel in humans. Further studies are needed to confirm that supra nutritional or pharmacologic intakes of nickel can affect carbohydrate, lipid and bone metabolism differently from physiological intakes that prevent changes caused by nickel deprivation.

VI. **Silicon**

A. **General Properties and Possible Metabolic Functions**

Silicon has long been suspected to be a beneficial bioactive, if not essential, element for humans. According to a review by Becker et al.,\(^{355}\) Louis Pasteur predicted that silicon would be found to be an important therapeutic substance for many diseases. At the beginning of the 20th century, French and German reports suggested that Pasteur’s prediction would become fact. These reports described therapeutic successes in treating numerous diseases, including atherosclerosis, hypertension and dermatitis with sodium silicate, simple organic silicon compounds or tea made from the silicon-rich horsetail plant.\(^{155,156}\) Also, there was some thought that silicon was essential because, according to the review by Schwarz,\(^{156}\) an article in 1930 stated that silicic acid was recognized as a normal constituent of the human organism, primarily of connective tissue, and the opinion was stated that “silicic acid is for connective tissue approximately of the same importance as iron for red blood cells, namely that it is simultaneously a stimulant for its formation as well as a building material for this tissue.” However, by 1935, silicon in medicine and the concept of silicon’s essentiality faded into obscurity as a consequence of some therapeutic failures and inadequate
evidence for silicon’s being biologically active. For the next 40 years, silicon as consumed in the diet was generally considered a biologically inert, harmless, nonessential element for living organisms except for some lower forms of life (silicate bacteria, diatoms, radiolarians and sponges).

In 1970, silicon once again began to receive attention as possibly being essential. That is when Carlisle reported that silicon is uniquely localized in active growth areas in young bone of mice and rats. Using electron microprobe techniques, Carlisle found that the silicon concentration in bone was related to its maturity or degree of mineralization. In the early stages of bone development in bone growth areas, both silicon and calcium concentrations were very low. As osteoid tissue progressed toward mineralization, silicon and calcium concentrations rose congruently. However, when mineralization had progressed so that calcium was present in amounts found in bone apatite, silicon was just detectable. Carlisle suggested that silicon was involved in the initiation of calcification through some effect on the preosseous organic matrix. Subsequent studies by Carlisle indicated that silicon had an essential function that influenced bone formation by affecting cartilage composition, particularly collagen and glycosaminoglycan content.

Although apparent deficiency signs have been found for silicon, it generally is not accepted as an essential nutrient for higher animals and humans because it lacks a clearly defined specific biochemical function. In 1978, Schwarz described the difficulty in defining a biochemical function for silicon. Schwarz first suggested that silicon as an ether- or ester-like derivative of silicic acid had a cross-linking role in connective tissue. In the 1978 report, based on improved silicon analyses of connective tissue, Schwarz indicated that his suggestion needed to be redefined. His subsequent suggestion, because of the stability of the O-Si-O bond, was that silicon is involved in binding structures such as cell surfaces or macromolecules to each other. Recently many extracellular matrix proteins have been identified that provide a connection between cells and their surrounding matrix. This connection allows cells to monitor the composition and properties of the matrix and to respond to matrix alterations. Nielsen has suggested that silicon may be necessary for the interaction between one or more of these macromolecules and osteotrophic cells, resulting in effects on cartilage composition and ultimately cartilage calcification.

Birchall and Espie have suggested that the role of silicon in higher animals is to interact (as silicic acid) with aluminum species (e.g., Al(OH)) to form an aluminosilicate that prevents aluminum from competing for iron binding sites (e.g., in prolyl hydroxylase), which results in decreased function. Thus, in the absence of silicon (or in the presence of excess aluminum) collagen synthesis and structure are adversely affected, which would be the basis for the observed effects of apparent silicon deficiency (e.g., bone organic matrix changes, impaired wound healing). Experimental and epidemiological findings indicate that some of the beneficial actions of high intakes of silicon may be occurring through this mechanism. In addition to alleviating the toxicity of aluminum, high intakes of silicon apparently can be beneficial through facilitating the absorption or utilization of some essential minerals including copper, magnesium and zinc.

B. Basis for Sports Nutrition Interest

Maintaining bone and joint health is the major sports nutrition interest in silicon. Shortly after her discovery of the silicon changes during events leading to calcification in bone, Carlisle reported that silicon was required for normal development of bones in chicks. Leg bones of apparent silicon-deficient chicks (less than 3-mg/kg diet) compared with silicon-supplemented chicks (100 mg Si/kg diet as sodium metasilicate) were shorter and had smaller circumferences and thinner cortices. Femurs and tibias fractured more easily under pressure and the cranial bones appeared somewhat flatter. About the same time, Schwarz and Milne reported that compared with rats fed a 500-mg Si/kg diet (as sodium metasilicate), those fed a diet containing less than 5 mg Si/kg had impaired incisor pigmentation and skulls that were shorter with distorted bone structure around the eye socket. In both of these reports, the experimental animals were not growing optimally. In a follow-up report, Carlisle reported that chicks treated the same as in the 1972 study showed that silicon
deficiency decreased articular cartilage and water in long bones and decreased the hexosamine content of articular cartilage. Although these studies suggested that silicon is essential for higher animals, the suboptimal growth of the experimental animals and the high silicon supplementation could be interpreted as that the responses to silicon were possibly pharmacologic and thus were overcoming a dietary shortcoming of something other than a silicon deficiency. Nonetheless, the studies showed that a relatively high intake of silicon in the form of relatively soluble metasilicate had beneficial effects and no apparent toxic effects in young growing animals apparently in a suboptimal nutritional state. Living organisms generally are more sensitive to toxicity during growth and when under stress.

In 1980, Carlisle\textsuperscript{173,174} reported that bone and cartilage abnormalities still occurred in chicks that were fed improved diets resulting in near optimal growth. When compared with chicks fed a 250-mg Si/kg diet as sodium metasilicate, chicks fed diets containing 1 mg Si/kg had tibias with a lower percentage and total amount of hexosamine, a lower percentage of collagen and a smaller proliferation zone in the epiphyseal cartilage. The skulls of silicon-deficient chicks had stunted parietal, occipital and temporal bone areas and the bone matrix lacked the normal striated trabecular pattern. The nodular pattern of the bone arrangement in silicon-deficient skulls indicated a more primitive type of bone. Carlisle\textsuperscript{175} also reported that silicon affected the bone matrix components of skulls from 14-day-old chick embryos grown in culture. Collagen was decreased and non-collagenous protein was increased in bones grown in silicon-deficient culture; these bones also had decreased prolylhydroxylase activity. Recently, it was found that orthosilicic acid at physiological concentrations stimulates collagen type I synthesis in human osteoblast-like cells and enhances osteoblastic differentiation in culture.\textsuperscript{176}

Because the studies of both Schwarz and Carlisle were clouded by the use of high, possibly pharmacological, amounts of fairly soluble silicon for supplemental controls, the effects of silicon deprivation in rats were reexamined by Seaborn and Nielsen.\textsuperscript{177–179} In these studies, supplemented controls were fed a diet containing only 4.5–35 mg Si/kg as sodium metasilicate and compared with rats fed diets containing ≤2 mg Si/kg. These studies confirmed that silicon deprivation affects bone, hexosamine and collagen metabolism. Silicon deprivation decreased femur acid and alkaline phosphatase, and humerus hydroxyproline and plasma ornithine aminotransferase (a key enzyme in collagen synthesis). A recent study\textsuperscript{180} found that silicon deprivation decreased plasma osteopontin concentration, increased plasma sialic acid concentration and increased urinary helical peptide (bone collagen breakdown product) excretion. Also, the response of bone metabolism indicators to ovariectomy in young growing rats was generally lower in silicon-deprived than silicon-supplemented rats. It was concluded that the findings support the hypothesis that silicon has a biochemical function that affects bone growth processes before bone crystal formation, and this occurs by affecting bone collagen turnover and sialic acid-containing extracellular matrix proteins such as osteopontin.

Whether it is by affecting the formation and structure of collagen, the binding of macromolecules to cell receptor sites, or the utilization or absorption of some mineral affecting bone formation, there is evidence that increased silicon consumption is beneficial to bone health. Jugaiah Singh et al.\textsuperscript{181} reported that in a cross-sectional, population-based study (2847 participants), dietary silicon correlated positively and significantly with bone mineral density at all hip sites in men and premenopausal women, which suggests that increased silicon intake is associated with increased cortical bone mineral density in these populations.

C. Metabolism

The mechanisms involved in the intestinal absorption and blood transport of silicon are unknown. A study with guinea pigs indicated that silicon is absorbed mainly as monomeric silicic acid.\textsuperscript{182} In humans, monosilicic acid in foods and beverages is readily absorbed, penetrates all body fluids and tissues at concentrations less than its solubility (0.01%) and is excreted in urine.\textsuperscript{183} Some of the absorbed
monosilicic acid can come from food polymeric silica, which can be partly dissolved by fluids of the gastrointestinal tract. Silicon absorption in rats has been found to be affected by age, sex and the activity of various endocrine glands. Silicon is not protein-bound in plasma, where it is believed to exist almost entirely as undissociated monomeric silicic acid.185 Silicon entering the blood stream apparently is transferred rapidly to tissues and urine because the silicon concentration in blood remains relatively constant in the presence of divergent intakes.186 Recent analyses indicate that human serum contains 11–25 µg/dL.187,188 Connective tissues, including aorta, bone, skin, tendon and trachea, contain much of the silicon that is retained in the body.175,189 Absorbed silicon is mainly eliminated via the urine, where it probably exists as orthosilicic acid or magnesium orthosilicate.175,185 The upper limits of urinary excretion apparently are set by the rate and extent of silicon absorption and not by the excretory ability of the kidney because peritoneal injection of silicon can elevate urinary excretion above the upper limit achieved by dietary intake.182 This suggests that silicon homeostasis is controlled by absorption mechanisms in addition to excretory mechanisms. This suggestion is supported by the finding that in rats, guinea pigs, cattle and sheep, the urinary excretion of silicon increases with an increasing intake of siliceous substances, but reaches a maximum that is not exceeded by increasing the intake.190 Within 2 hours of ingestion of a trace dose of 32-silicon, uptake was complete in a healthy male.191 Within 48 hours, 36% of the dose was excreted in the urine and the elimination was nearly complete. Elimination occurred by two simultaneous first-order processes with half-lives of 2.7 and 11.3 hours, representing about 90% and 10%, respectively, of the total output. It was suggested that the rapidly eliminated silicon was probably retained in the extracellular fluid volume, while the slower component may have represented intracellular uptake and release. In another study of silicon kinetics,192 silicon peaked in blood about 1 hour after an intake of 27–55 mg orthosilicic acid/L of water in eight healthy adults. Renal clearance was 82–90 mL/min, which is similar to that found earlier.185 These clearances suggest a high renal filtration.

D. DIETARY AND SUPPLEMENTAL SOURCES

The form of dietary silicon has a major influence on its absorption. For example, humans absorbed about 1% of a large dose of an aluminosilicate compound but absorbed >70% of a single dose of methylsilanetriol, a drug developed for the treatment of circulatory ischemia.193 Silicon was found to be absorbed better from stabilized orthosilicic acid than from herbal silica (Equisetum arvense extract) or colloidal silicic acid.188 Early balance studies with animals indicated that almost all ingested silicon is unabsorbed. The finding of low absorption probably resulted from the intake of highly unavailable silicon and the intake of silicon that exceeded the amount needed to achieve maximal absorption. Thus, these studies may be misleading about the bioavailability of silicon when consumed in low or mg quantities in various foods. Recently, it was found that an average of 41% of dietary silicon was excreted in the urine (an indicator of absorption).194 Silicon in grains and grain products was readily absorbed, as indicated by a mean urinary excretion of 49 ± 34% of intake. In several of the grain products, silicon was as available as it was from fluids. For example, urinary silicon excretion was 41–86% from corn flakes, white rice and brown rice and 50–86% from mineral waters. Silicon in fruits and vegetables, except green beans and raisins, was readily absorbed, with a mean urinary excretion of 21 ± 29% of intake. Some forms of dietary fiber may affect silicon bioavailability because in humans, a diet high in fiber from fruits and vegetables significantly depressed silicon balance.195

The average daily intakes of silicon apparently range from 20–50 mg/day.196 The richest sources of silicon are unrefined grains of high fiber content, and cereal products, including beer. Meat, fish and dairy products are poor sources of silicon. A source of oral silicon is additives to prepared foods, confections and pharmaceuticals. Amorphous silicates are considered safe additions to foods. Their use as anti-caking agents, for example, is permitted up to 2% by weight. A generally recognized as safe (GRAS) committee concluded that silicates added to foods to enhance physical properties are relatively inert and thus not bioavailable.
E. SUPPLEMENTATION

Silicon is another element for which there has been very little recent effort to ascertain whether supplementation would have beneficial effects in humans, apparently because of the lack of a defined biochemical function and indicators of silicon status.

Ingested silicon has a relatively low order of toxicity. About the only pathological condition that may occur with a high intake of silicon is urolithiasis. Most silicon compounds, especially silicon dioxide compounds, are essentially nontoxic to humans when taken orally. Magnesium trisilicate, an over-the-counter antacid, has been used by humans for more than 40 years with only minimal apparent deleterious effects reported. In addition to urolithiasis, a high intake of silicon may interfere with the absorption or utilization of some essential nutrient, particularly zinc. An antagonism between zinc and silicon results in high dietary silicon’s decreasing the zinc concentrations in plasma and tissues of rats.  The amount of dietary silicon used to show the antagonism was extremely high in one study; the rats were fed 400 mg Si/kg body weight as sodium metasilicate in drinking water for the last 6 weeks of an 18-week experiment. In the other study, the effect of a 270-mg Si/kg diet as tetraethylorthosilicate on decreasing plasma zinc was significant only in zinc-deficient rats.

Because of the inadequacy of available data, the FNB established no UL for silicon. In the United Kingdom, a safe upper level of 12 mg/kg body weight/day has been suggested for humans. This level was based on an animal study in which a no-observed-adverse-effect-level (NOAEL) of a 50,000-mg/kg diet of supplemental dietary silica, equivalent to 2500 mg/kg body weight/day in rats and 7500 mg/kg body weight/day in mice was found. This seems to be a conservative value, considering the NOAEL and that intakes of 35–45 mg Si/kg body weight/day has been found beneficial for bone and brain health in experimental animals. Based on the latter finding, a safe silicon intake for a 70-kg man probably is greater than 2 g/day.

F. DIETARY RECOMMENDATIONS

The FNB set no dietary reference intakes (DRI) for silicon. On the basis of weak balance data, a recommended silicon intake of 30–35 mg/day was suggested for athletes; this was 5–10 mg higher than for non-athletes. Based on extrapolations from animal data, Seaborn and Nielsen speculated that a recommended intake may be between 5 and 10 mg/day. Others have suggested that a daily minimum requirement may be near 10–25 mg based on the amount excreted in urine in 24 hours.

G. FUTURE RESEARCH DIRECTIONS OR NEEDS

Before any dietary or supplement recommendations can be made for physically active people, much needs to be learned about silicon. Foremost is the need to establish a biochemical function or mechanism through which silicon is beneficial to bone. Knowledge of the function or mechanism would facilitate the development of silicon status indicators and the assessment of the effects of low and supra nutritional dietary silicon intakes in humans. Silicon status indicators are needed to determine whether a low silicon status that responds to increased silicon intakes is a significant sports nutritional concern.

VII. VANADIUM

A. GENERAL PROPERTIES AND POSSIBLE METABOLIC FUNCTIONS

Since the turn of the 19th century, when some French physicians suggested vanadium was a panacea for human disorders, vanadium has been proposed numerous times to be of pharmacological or nutritional importance. The hypothesis that vanadium has a physiological or essential role in higher animals and humans has gone through periods where it has received much credence then followed
by much skepticism.\textsuperscript{201} At present, vanadium is generally not accepted as an essential nutrient because a specific biochemical function has not been defined for vanadium at physiological intakes.

There is no question that vanadium is a bioactive element. Its ability to selectively inhibit protein tyrosine phosphatases at submicromolar concentrations probably explains the broad range of effects that high intakes causing elevated tissue vanadium concentrations have on cellular regulatory cascades.\textsuperscript{202} Protein tyrosine phosphatase inhibition is thought to be the basis for vanadium's having insulin-like actions at the cellular level and stimulating cellular proliferation and differentiation. The insulin-mimetic action of vanadium has resulted in an effort to develop vanadium compounds that could be therapeutic agents for diabetes.\textsuperscript{203} In addition to having effects at pharmacological intakes, vanadium may affect phosphorylation/dephosphorylation at physiological or nutritional intakes such that a regulatory cascade is altered. This may be the basis for observations that vanadium deprivation altered thyroid hormone metabolism,\textsuperscript{201,204} impaired reproduction\textsuperscript{205} and altered bone morphology.\textsuperscript{205,206}

Vanadium is essential for some lower forms of life where it is required for some enzymes.\textsuperscript{207} Vanadium-dependent bromoperoxidases have been found in a number of marine brown algae, marine red algae and a terrestrial lichen. Vanadium-dependent iodoperoxidases have been detected in brown seaweeds, and a vanadium-dependent chloroperoxidase has been identified in the fungus Curvularia inaequalis. These haloperoxidases catalyze the oxidation of halide ions by hydrogen peroxide, thus facilitating the formation of a carbon–halogen bond. The enzymatic roles for vanadium in lower forms of life suggest the possibility that vanadium has a similar role in higher forms of life.

### B. Basis for Sports Nutrition Interest

#### 1. Insulinomimetic Actions

The insulin-like actions of vanadium have been well reviewed.\textsuperscript{203,208} According to these reviews, the anti-diabetic effect of vanadium was first reported more than 100 years ago, but its potential as an orally active insulin-mimetic agent was stimulated by reports beginning in 1985. Since then, studies with animal models of type 1 diabetes showed that chronic treatment with vanadium salts lowered plasma glucose concentration, increased peripheral glucose utilization and normalized hepatic glucose output, but had no effect on plasma insulin concentration. One of the reviews\textsuperscript{203} noted that the vanadium supplementation had no or minor effects on plasma glucose and insulin concentrations in normal control animals. Treatment of human patients with type 1 diabetes reduced insulin requirements. Several organic vanadium compounds have been developed and, in addition to inorganic vanadium compounds, have been examined as potential therapeutic agents for type 2 diabetes. The vanadium compounds significantly decreased plasma insulin concentrations and improved insulin sensitivity in several animal models of insulin resistance and type 2 diabetes. Oral treatment of type 2 diabetic humans with vanadium reduced fasting plasma glucose concentrations, suppressed hepatic glucose production and improved insulin sensitivity in skeletal muscle. Treatment with vanadyl sulfate had no effect on insulin sensitivity and fasting plasma glucose and insulin concentrations in healthy adults; an observation made for several animal models. The mechanisms through which vanadium has insulin-mimetic actions are not completely understood. Suggested mechanisms include inhibition of key gluconeogenic enzymes and the inhibition of protein tyrosine phosphatases. Vanadium inhibition of protein dephosphorylation would indirectly enhance insulin receptor or insulin receptor substrate phosphorylation and thus its action.

The amounts of vanadium used in animals to show insulin-mimetic actions were extremely high relative to normal intakes. In some cases, the intakes were toxic and caused poor growth and diarrhea. The vanadium doses in human experiments were about 100-fold lower than those used for most studies of diabetic animal models. Still, the doses used (e.g., 100 mg vanadyl sulfate or 125 mg sodium metavanadate per day\textsuperscript{209–212}) were an order of magnitude greater than possible nutritional needs (described below).
Insulin has an anabolic effect on skeletal muscle and other tissues through promoting amino acid uptake and protein synthesis while retarding protein degradation. Thus, reports that vanadium has efficacy in some animal models of both type 1 and type 2 diabetes was quickly extrapolated by supplement marketers as evidence that vanadium has anabolic effects and thus can be used to enhance muscle building, strength and performance. This thought persists now, although it has been shown that not all effects of insulin are mimicked by vanadium; the exceptions include that of vanadium’s not affecting amino acid uptake and protein synthesis. Also, the promotion of vanadium supplements ignores the finding that vanadium has no marked insulin-like effect on healthy animals and humans.

2. Bone and Joint Health Promotion

One of the first vanadium-deprivation signs reported for chicks was adverse effects on bone development. Histological examination of the tibias from vanadium-deprived chicks revealed severe disorganization of the cells of the epiphysis. The cells appeared compressed and their nuclei flattened. These abnormalities apparently were the reason that vanadium-deprived chicks had a shortened, thickened leg structure. Bone abnormalities were also found in vanadium-deprived goats. Compared with goats fed a 0.5–2 mg V/kg diet, goats fed less than 10 µg/kg diet exhibited pain in the extremities, swollen forefoot tarsal joints and skeletal deformations in the forelegs. These changes in bone suggest that vanadium may have a role that affects bone or connective tissue metabolism. This suggestion is supported by the finding that vanadium stimulated the mineralization of bones and teeth and the repair of bones. Orthovanadate stimulates bone cell proliferation and collagen synthesis in vitro. Also, orthovanadate increased phosphotyrosine levels and inhibited collagenase production by chondrocytes in vitro. Recent studies suggest that the mechanism through which vanadium affects bone metabolism is through modifying phosphorylation/dephosphorylation reactions that affect growth factor action. Vanadium supplementation reverses many of the symptoms of osteoporosis caused by high-dose glucocorticoids in adult rats. Osteoblasts are mitogenically repressed by high-dose glucocorticoids and this correlates with decreased extracellular signal-regulated kinase (ERK) activation in response to growth factors. Vanadate restores sensitivity to growth factors at the levels of both ERK activation and cell proliferation.

In the experiments showing that vanadium had a beneficial effect on bone, the amounts of vanadium used in supplemented animals and cells were high relative to those that may be needed nutritionally. For example, in the chick and goat deprivation studies, the supplemented controls were fed diets containing 0.5–3.0 mg V/kg; apparent nutritional deficiency signs required feeding diets containing less than 25 µg/kg diet. The diets used may have been unbalanced in some nutrients. Thus, one cannot dismiss the possibility that the high vanadium supplementation was acting pharmacologically to overcome bone changes induced by something other than a simple vanadium deficiency. Such a possibility is supported by the finding that a 0.5-mg V/kg diet increased plasma cortisol in guinea pigs, which indicates that vanadium was a stressor, or acting in a non-nutritional manner. These guinea pigs also exhibited increased bone calcium and magnesium concentrations. Further study is required to establish whether low dietary vanadium intakes increase the susceptibility to bone loss and whether supra nutritional intakes of vanadium can help prevent bone loss in conditions where phosphatase activity is excessive.

C. Metabolism

Most ingested vanadium is unabsorbed and is excreted in the feces. Because very low concentrations of vanadium, generally <0.8 µg/L, are found in urine, compared with estimated daily intakes of 12–30 µg and the fecal content of vanadium, apparently <5% of vanadium ingested normally is absorbed. Animal studies generally support the concept that vanadium is poorly absorbed. However, some results from rats indicate that vanadium absorption can exceed 10%
under some conditions, a finding that suggests caution in assuming that ingested vanadium is always poorly absorbed from the gastrointestinal tract.\textsuperscript{221}

Most vanadium that is absorbed is probably transformed in the stomach to the vanadyl ion and remains in this form as it passes into the duodenum.\textsuperscript{222} The mechanisms involved in the absorption of vanadium in the cationic or vanadyl (VO\textsuperscript{2+}) form are unknown. In vitro studies suggest that vanadium in the anionic or vanadate (HVO\textsubscript{4}\textsuperscript{2−}) form can enter cells through phosphate or other anion transport systems.\textsuperscript{223} Vanadate is absorbed three to five times more effectively than vanadyl.\textsuperscript{224} Apparently the different absorbability rates for vanadate and vanadyl, the effect of other dietary components on the binding and forms of vanadium in the stomach and the rate at which vanadate is transformed into vanadyl markedly affect the percentage of ingested vanadium absorbed. Other dietary substances that apparently affect the binding and forms of vanadium in the stomach include chromium, protein, ferrous ion, chloride and aluminum hydroxide.\textsuperscript{220}

When vanadate appears in the blood, it is quickly converted into the vanadyl cation.\textsuperscript{225} However, as a result of oxygen tension, vanadate still exists in blood. Vanadyl, the most prevalent form of vanadium in blood, is bound and transported by transferrin and albumin.\textsuperscript{222} Vanadate is transported by transferrin only.\textsuperscript{226} Vanadyl also complexes with ferritin in plasma and body fluids.\textsuperscript{227,228} It remains to be determined whether vanadyl-transferrin can transfer vanadium into cells through the transferrin receptor or whether ferritin is a storage vehicle for vanadium. Vanadium is rapidly removed from plasma and is generally retained in tissues under normal conditions at concentrations less than 10 ng/g fresh weight.\textsuperscript{220} Bone apparently is a major sink for excessive retained vanadium.

Excretion patterns after parenteral administration\textsuperscript{229,230} indicate that urine is the major excretory route for absorbed vanadium. However, a significant portion of absorbed vanadium may be excreted through the bile.\textsuperscript{229}

D. Dietary and Supplemental Sources

Typical human diets generally supply <30 μg V/day.\textsuperscript{220} Foods rich in vanadium (>40 ng/g) include shellfish, mushrooms, parsley, black pepper and some prepared foods. Cereals, liver and fish tend to have intermediate amounts of vanadium (5–40 ng/g). Beverages, fats and oils, fresh fruits and fresh vegetables generally contain <5 ng/g and often <1 ng/g.\textsuperscript{220}

Upon the erroneous extrapolation of insulin-mimetic effects of vanadium to having anabolic effects on skeletal muscle, a proliferation of powders, beverages, formulas and supplements containing alarming amounts of vanadium appeared in the market. These supplements contained quantities of vanadium that could result in some individuals consuming more than the 1.8 mg/day UL set by the FNB.\textsuperscript{51} and sometimes approaching the 14–20 mg/day that was found to have toxic effects in humans.\textsuperscript{220}

E. Supplementation

Although there have been several studies examining the response of diabetic subjects to vanadium supplementation (see above), only a few have examined the effect of vanadium supplementation on strength, performance and bone and heart health indices of healthy adults. Fawcett et al.\textsuperscript{231} determined the effect of supplemental 0.5 mg vanadyl sulfate/kg body weight/day on body composition and performance in a study involving 40 individuals using weight training as part of their fitness program; 31 completed the 12-week, double-blind, placebo-controlled study. It was concluded that the vanadium supplement was ineffective in changing body composition in weight-training athletes. There was a significant vanadium effect in one performance variable (leg extension), but this finding was compromised by the fact that the vanadium-supplemented group started at a lower baseline than the placebo group. Thus, this modest performance-enhancing effect requires confirmation. About 20% of the subjects taking the vanadium supplement reported the side effect of fatigue.
Compared with elements such as silicon and manganese, vanadium is a relatively toxic element for humans. As indicated in the following, the threshold level for toxicity through ingestion apparently is between 10–20 mg/day. Schroeder et al. fed 15 subjects 4.5 and 9 mg V/day as diammonium oxysulfatoxyvanate for 6–16 months without apparent detrimental effect. Curran et al. fed five subjects 13.5 mg/day in three divided doses as diammonium oxysulfatoxyvanate for 6 weeks; no sign of intolerance or toxicity was found. In contrast, Sommerville and Davis supplemented 12 subjects 13.5 mg/day for 2 weeks and then 22.5 mg V/day for 5 months as diammonium vanadotartrate; five patients exhibited persistent upper abdominal pain, anorexia, nausea and weight loss. Dimond et al. supplemented ammonium vanadyl tartrate orally to six subjects for 6–10 weeks in amounts ranging from 4.5–18 mg V/day; green tongue, cramps and diarrhea were observed at the larger doses. Based on renal effects in experimental animals, the FNB set an UL of 1.8 mg/day for adults ≥ 19 years of age.

**F. Dietary Recommendations**

The FNB set no RDA for vanadium. However, based on animal studies, any human requirement to prevent deficiency pathology for vanadium would be small. A daily dietary intake of 10–15 μg probably would meet any postulated requirement.

**G. Future Research Directions or Needs**

Research is needed to determine the validity of having supplements containing high amounts of vanadium in the marketplace. This research should definitively establish the toxicity threshold for vanadium and determine whether long-term high consumption of vanadium could lead to pathological disorders such as hypertension. Studies are needed to determine whether supra nutritional, but non-toxic, intakes of vanadium enhance athletic performance or bone health. Definition of a biochemical function for vanadium at physiological intakes is needed before this element can be considered essential. Definition of an essential function would help differentiate between nutritional and pharmacological actions of vanadium and could be used to determine whether low dietary intakes of vanadium are of practical nutrition concern for the general public in addition to athletes. It is obvious that it is premature to recommend vanadium supplements for enhancing strength, muscle mass and athletic performance.

**VIII. SUMMARY**

Although boron, manganese, molybdenum, nickel, silicon and vanadium are not considered significant nutritional minerals, they have received some attention in the sports nutrition field because of findings suggesting that they could enhance strength, performance or endurance in athletic activities. Most of these findings have come from experimental animals and have not been substantiated by carefully controlled human studies. At present, there is inadequate evidence to suggest that increasing the intake or consuming supra nutritional amounts of any of these six minerals would be of benefit for athletic performance or increasing muscle mass. However, findings from animal experiments and limited clinical studies suggest that further study is needed to determine whether increased intakes of one or more of these elements would be of benefit for the physically active person. Some of the more intriguing possible studies based on these findings would be those determining whether a safe (non-toxic) supra nutritional intake of boron enhances bone strength, energy utilization, or endurance; manganese enhances energy utilization or endurance; nickel enhances energy utilization or bone strength, silicon enhances bone strength; or vanadium enhances energy utilization or bone strength. Also of interest would be the determination of whether low intakes of any of these elements result in an impairment in athletic performance, bone strength or endurance that could be overcome by diets providing nutritionally adequate amounts of the element.
REFERENCES


