

## Nickel

**M**onovalent, divalent, and trivalent forms of nickel occur in living organisms. In a tightly bound form, the divalent form ( $\text{Ni}^{2+}$ ) is required for the activity of urease, an enzyme found in plants and micro-organisms. Trivalent nickel is used for enzymatic hydrogenation, desulfurization, and carboxylation reactions in anaerobic micro-organisms. The redox action of nickel in some of these reactions might involve the monovalent form. Divalent nickel may be the most important in nutrition because it can complex, chelate, or bind many substances of nutritional interest, especially amino acids and proteins. During the 1970s and 1980s when the definition of essentiality was less rigorous, nickel often was considered an essential nutrient for animals. At present, nickel is generally not considered an essential nutrient for higher animals and humans because it lacks a clearly defined specific biochemical function nor has a low dietary intake been definitively shown to interrupt the life cycle.

Seven of the eight enzymes for which nickel has been found to be essential in plants and micro-organisms are involved in the use or production of the gases ammonia, hydrogen, carbon monoxide, carbon dioxide, methane, and oxygen (1). The other enzyme, glyoxalase I, is used to convert methylglyoxal, a potent cytotoxic compound, to lactate (2). Enzymes found in these lower forms of life suggest the possibility that nickel might have beneficial bioactivity in higher forms of life by affecting the function or formation of gaseous molecules or activity of the intestinal microbiome. There are findings that support this possibility. Nickel has a stabilizing effect on hypoxia-inducible factor-1 $\alpha$  protein and activates hypoxia-inducible gene expression (3), which affects glucose metabolism and osteogenesis; these have been found to be affected by a low nickel intake in animal experiments. Nickel also potently induces the activity of heme oxygenase (4) that produces carbon monoxide, an activator of guanylate cyclase that produces cyclic guanylate monophosphate (cGMP). The cGMP signal transduction system has a critical role in vision, taste, smell, blood pressure control, kidney function, and sperm motility, all which have been found to be affected by a low nickel intake in animal experiments (5, 6).

Other suggestions that have been given for the beneficial bioactivity of nickel include performing actions normally done by iron and influencing intracellular calcium content and its signaling (7). Nickel also might have desirable effects on methyl metabolism. Nickel is required for the formation of factor F<sub>430</sub>, a tetrapyrrole similar in structure to vitamin B-12, which is a component of methyl coenzyme M reductase. This enzyme is involved in methane formation in anaerobic bacteria. Nickel has been found to have a cooperative relationship with vitamin B-12 (8) and to ameliorate an increase in serum homocysteine in vitamin B-12-deficient pigs (9). However, at

present, no mechanism has been definitively described for the numerous reported beneficial effects of nickel found in animal experiments.

### Deficiencies

Although nickel has not been established as an essential nutrient for higher forms of life, nutritional and supra-nutritional amounts of nickel have been shown to have beneficial effects on several physiological and biochemical systems apparently impaired in experimental animals deprived of nickel in their diet (7). These impairments include decreased sperm production and motility, decreased strength and altered composition of bone, increased plasma lipids and decreased serum glucose, and decreased iron status and utilization in rats. Nutritional amounts of nickel added to a diet deprived of nickel also alleviated impaired special senses of vision, olfaction, and taste in rats; renal damage and high blood pressure induced in rats fed a high-salt diet; and vitamin B-12 deficiency and high blood homocysteine concentrations in pigs. The effect of low dietary intakes of nickel by humans remains unstudied. However, serum nickel was negatively correlated with plasma total homocysteine in hemodialysis patients (10).

### Diet Recommendations

Neither Recommended Dietary Allowances nor Adequate Intakes have been established for nickel (11). The Tolerable Upper Intake Levels set for nickel as soluble salts (milligrams/day) in the United States and Canada are for children aged 1–3 years (0.2), 4–8 years (0.3), and 9–13 years (0.6) and for adults (1.0). Based on animal findings, a beneficial intake of nickel for humans would be <100  $\mu\text{g}/\text{d}$  and has been suggested to be as low as 25–35  $\mu\text{g}/\text{d}$  (12). Most individuals achieve this intake because typical daily dietary intakes for nickel are >70  $\mu\text{g}/\text{d}$  (11). The Food and Drug Administration has not established Daily Values for nickel to be used for food and dietary supplement-labeling purposes.

### Food Sources

Foods of animal origin are low in nickel while foods of plant origin are generally high in nickel. Rich sources of nickel include chocolate, nuts, dried beans and peas, and grains (11). Diets high in these foods could supply >900  $\mu\text{g}/\text{d}$  of nickel. However, typical daily dietary intakes for nickel are 70–400  $\mu\text{g}/\text{d}$  (11).

### Clinical Uses

Nickel is not used for clinical purposes.

### Toxicity

The toxicity of nickel through oral intake is low (12). The basis for this is that intestinal absorption with food is low

(<10%). However, a much higher percentage, up to 50% but usually closer to 20% to 25%, of the dose is absorbed when a nickel salt is ingested in water after an overnight fast. Nickel is rapidly excreted via the kidney. Nickel has little tendency to accumulate in tissues of animals and humans. Thus, life-threatening toxicity of nickel through oral intake is unlikely. Generally,  $\geq 250 \mu\text{g}$  nickel/g of diet is needed to produce signs of nickel toxicity (e.g., depressed growth) in rats, mice, chickens, rabbits, and monkeys (12). However, a moderate intake of nickel under special conditions possibly could affect health (12). Moderate amounts of dietary nickel have been found to exacerbate iron and copper deficiencies in rats. Ingestion of moderate amounts of nickel may be of importance in maintaining eczema caused by nickel allergy. An oral dose as low as  $600 \mu\text{g}$  as nickel sulfate in water (thus, highly available) produced a positive reaction in some nickel-sensitive individuals. This dose is in the range of intakes as indicated above.

### Recent Research

Research on the beneficial effect or nutritional importance of nickel has been essentially nonexistent in the past decade. Recent research mostly focuses on nickel mechanisms resulting in allergy, the role and use of nickel in known nickel enzymes, nickel's beneficial effect on nitrogen utilization in plants, and the determination of its presence in food and tissues.

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