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Arsenic, Boron, Nickel, Silicon, and Vanadium

SUMMARY

An Estimated Average Requirement (EAR) or Adequate Intake (AI) was not set for arsenic, boron, nickel, silicon, or vanadium. In the case of the vitamins and other minerals reviewed in this report, there are well-established studies typically based on observations from several laboratories. The data currently available for these vitamins and other minerals provide an understanding of the metabolic role of each and describe the consequences of their restriction in the diets of both laboratory animals and humans. There are also clearly defined, readily reproducible indicators in humans for these vitamins and other minerals that can be used to determine an EAR and calculate a Recommended Dietary Allowance, or to establish an AI. At present, such data do not exist for arsenic, boron, nickel, silicon, and vanadium.

In the case of arsenic, boron, nickel, silicon, and vanadium, there is evidence that they have a beneficial role in some physiological processes in some species. For boron, silicon, and vanadium, measurable responses of human subjects to variations in dietary intake have also been demonstrated. However, the available data are not as extensive (e.g., dose-response data are absent) and the responses are not as consistently observed as they are for the vitamins and other minerals. Thus, data are insufficient to determine an EAR for any of these minerals.

Estimates of dietary intakes of arsenic, boron, nickel, silicon, and vanadium by the North American adult population are available

and could have been used to establish an AI. However, establishing an AI also requires a clearly defined, reproducible indicator in humans sensitive to a range of intakes. Indicators that meet this criterion for establishing an AI are not currently available for any of these minerals, and therefore no AI was set.

Notwithstanding, observations of deficiency effects (e.g., on growth and development) in multiple animal species and data from limited human studies suggest beneficial roles for arsenic, boron, nickel, silicon, and vanadium in human health. These data clearly indicate a need for continued study of these elements to determine their metabolic role, identify sensitive indicators, and more fully characterize specific functions in human health.

Estimates of Tolerable Upper Intake Levels (UL) were set for boron, nickel, and vanadium. The ULs for boron and vanadium are based on animal data and have been set for adults at 20 mg/day and 1.8 mg/day, respectively. The UL for nickel is 1 mg/day. There were insufficient data using the model described in Chapter 3 to set a UL for arsenic and silicon.

ARSENIC

BACKGROUND INFORMATION

Function

There have been no studies to determine the nutritional importance of arsenic for humans. Although the metabolic function of arsenic is not well understood, one study in rats suggests that arsenic may have a role in the metabolism of methionine (Uthus and Poellot, 1992). Arsenic deprivation was associated with an increase in hepatic S-adenosyl-homocystine concentrations and a decrease in hepatic S-adenosyl-methionine concentrations. Arsenic deprivation has also been associated with impaired growth and abnormal reproduction in rats, hamsters, chicks, goats, and miniature pigs (Anke, 1986; Uthus, 1994). Arsenic has also been suggested to be involved with the regulation of gene expression (Meng and Meng, 1994). Arsenite is associated with changes in the methylation of core histones and therefore is active at the transcriptional level (Desrosiers and Tanguay, 1986).

Physiology of Absorption, Metabolism, and Excretion

The absorption of inorganic arsenic is related to the solubility of the compound ingested (Vahter, 1983). In humans, more than 90 percent of inorganic arsenite and arsenate from water is absorbed (Vahter, 1983), and approximately 60 to 70 percent of dietary arsenic is absorbed (Hopenhayn-Rich et al., 1993). Once absorbed, inorganic arsenic is transported to the liver where it is reduced to arsenite and then methylated. The majority of ingested arsenic is rapidly excreted in the urine. The proportion of the various forms of arsenic in urine can vary; however, the common forms present are inorganic arsenic, monomethylarsonic acid, dimethylarsinic acid, and trimethylated arsenic (Yamato, 1988).

FINDINGS BY LIFE STAGE AND GENDER GROUP

Because of the lack of human data to identify a biological role of arsenic in humans, neither an Estimated Average Requirement, Recommended Dietary Allowance, nor Adequate Intake were established.

INTAKE OF ARSENIC

Food Sources

Dairy products can contribute as much as 31 percent of arsenic in the diet; meat, poultry, fish, grains and cereal products collectively contribute approximately 56 percent (Mahaffey et al., 1975). Based on a national survey conducted in six Canadian cities from 1985 to 1988, it was reported that foods containing the highest concentrations of arsenic were fish (1,662 ng/g), meat and poultry (24.3 ng/g), bakery goods and cereals (24.5 ng/g), and fats and oils (19 ng/g) (Dabeka et al., 1993). The substantial portion of arsenic present in fish is in the organic form. The major contributors of inorganic arsenic are raw rice (74 ng/g), flour (11 ng/g), grape juice (9 ng/g), and cooked spinach (6 ng/g) (Schoof et al., 1999).

Dietary Intake

Results of the analysis of 265 core foods conducted by the Food and Drug Administration (1991–1997), and analysis of foods and intake data from the U.S. Department of Agriculture Continuing Survey of Food Intakes by Individuals (1994–1996), indicate that

the intakes of arsenic for all age groups ranged from 0.5 to 0.81 µg/kg/day (Gunderson, 1995) and that the median intake of arsenic by adult men and by women was approximately 2.0 to 2.9 µg/day and 1.7 to 2.1 µg/day, respectively (Appendix Table E-2). Adams and coworkers (1994) reported lower intakes for adults (23 to 58 µg/day) from 1982 to 1991. There was not a marked difference in the arsenic consumption between various age groups. Gartrell and coworkers (1985) reported a similar mean U.S. intake of arsenic of 62 µg/day, and Tao and Bolger (1999) reported intakes ranging from 28 to 72 µg/day for adults from 1987 to 1988.

Data on the concentration of arsenic in human milk are limited; however, studies have reported mean concentrations ranging from 0.2 to 6 µg/kg wet weight (Byrne et al., 1983; Dang et al., 1983; Grimanis et al., 1979).

TOLERABLE UPPER INTAKE LEVELS

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects. Arsenic is currently under investigation for the treatment of leukemia (Look, 1998).

Arsenic occurs in both inorganic and organic forms, with the inorganic forms that contain trivalent arsenite (III) or pentavalent arsenate (V) being of the greatest toxicological significance (Chan and Huff, 1997). No data on the possible adverse effects of organic arsenic compounds in food were found. Because the organic forms are usually less toxic than the inorganic (ATSDR, 1998), adverse effects of inorganic forms are described. It is unclear whether risk assessments should be developed for specific groups of inorganic arsenic compounds.

Adverse Effects

The adverse effects of arsenic in humans have been identified with exposure to inorganic arsenic, although in animals higher exposures to organic arsenic produces some of the same effects as

lower exposures to inorganic arsenic (ATSDR, 1998). There is some evidence that arsenic III may be more toxic than arsenic V (Byron et al., 1967; Maitani et al., 1987). Animals do not appear to be good quantitative models for inorganic arsenic toxicity in humans (ATSDR, 1998), perhaps because of the species diversity of erythrocyte-binding of arsenic and inorganic arsenic methyltransferase activity, a detoxification mechanism (Aposhian, 1997; Goering et al., 1999).

Acute Effects

Inorganic arsenic is an established human poison. Ingestion of doses greater than 10 mg/kg/day leads to encephalopathy and gastrointestinal symptoms (Civantos et al., 1995; Levin-Scherz et al., 1987; Quatrehomme et al., 1992). Poisoning also occurs with arsenic doses of 1 mg/kg/day or greater and can be accompanied by anemia and hepatotoxicity (Armstrong et al., 1984; Fincher and Koerker, 1987).

Arsenicism

Chronic intake of 10 µg/kg/day or greater of inorganic arsenic produces arsenicism, a condition characterized by alteration of skin pigmentation and keratosis (NRC, 1999). In some regions, an occlusive peripheral vascular disease also occurs resulting in gangrene of the extremities, especially of the feet, thus termed blackfoot disease (Engel and Receveur, 1993; Tseng, 1977). It has been hypothesized that zinc deficiency may exacerbate the toxicity of arsenic (Engel and Receveur, 1993). Malnutrition has been associated with an increased risk of blackfoot disease (Yang and Blackwell, 1961). Because arsenicism may be associated with arsenic intakes higher than those causing other adverse effects (see "Carcinogenicity"), it was not selected as a critical adverse effect to set a UL.

Peripheral Neuropathy

Intermediate and chronic exposures of arsenic up to levels of 11 mg/L of water are associated with symmetrical peripheral neuropathy (Franzblau and Lilis, 1989; Huang et al., 1985; Wagner et al., 1979). However, in some populations exposures of 5 mg/L of water did not result in clinical or subclinical neuropathy (Kreiss et al., 1983).

Developmental Toxicity

Developmental effects in humans have not been demonstrated (ATSDR, 1998; NRC, 1999). In the hamster, single intragastric doses of 1.4 mg of arsenic/kg to pregnant females led to fetal mortality (Hood and Harrison, 1982). In the mouse, fetal mortality and teratogenicity were produced by single intragastric doses of 6 to 7 mg/kg (Hood, 1972) and 11 mg/kg (Hood and Bishop, 1972); oral doses of 23 mg/kg (Baxley et al., 1981) had the same effects. In the rat, an intraperitoneal dose of 5 to 10 mg/kg produced a high percentage of malformed fetuses (Beaudoin, 1974).

Genotoxicity

Sodium arsenite induced point mutations in two strains of *Escherichia coli* WP2; negative results were obtained in a *recA* strain. Arsenic trichloride and sodium arsenite gave positive results in a *rec* assay in *Bacillus subtilis* (Nishioka, 1975). Positive results were also obtained in this assay with arsenic trioxide and arsenic pentoxide (Kanematsu et al., 1980). Sodium methanearsonates were negative in this assay (Shirasu et al., 1976).

Potassium and sodium arsenite caused mitotic arrest and chromosomal aberrations, including chromatid gaps, breaks, translocations, dicentrics, and rings in cultured human peripheral leukocytes and human diploid fibroblast WI.38 and MRC5 lines (Oppenheim and Fishbein, 1965; Paton and Allison, 1972).

Some of the mutagenic effects of arsenic may be a consequence of the formation of reactive oxygen species (Hei et al., 1998).

Carcinogenicity

Ingestion of inorganic arsenic is associated with risk of cancers of the skin, bladder, and lung (IARC, 1980, 1987; NRC, 1999). Increased risks of other cancers such as kidney and liver have also been reported, but the strength of the association is not great (NRC, 1999). There are no studies of cancer in humans after exposure to organic arsenicals (ATSDR, 1998).

Most studies of a positive association with cancer involve intake of inorganic arsenic in drinking water. A large-scale survey of 40,421 inhabitants (19,269 men and 21,152 women) of an area on the southwest coast of Taiwan, where artesian well water with a high concentration of arsenic was consumed for more than 45 years, found that the overall prevalence rates for skin cancer, hyper-

pigmentation, and keratosis were 10.6, 183.5, and 71.0/1,000, respectively (Tseng et al., 1968). They also found that the male-to-female ratio for skin cancer was 2.9:1 and 1.1:1 for hyperpigmentation and keratosis. The prevalence appeared to increase progressively with age for all three conditions, although there was a decline in cancer and hyperpigmentation in women older than 69 years of age. The prevalence rates for skin cancer, hyperpigmentation, and keratosis showed an ascending gradient which correlated with the arsenic content of the well water. Blackfoot disease had an overall prevalence rate of 8.9/1,000 and, similar to skin cancer, displayed a dose-response relationship with the amount of arsenic in the well water. There was a significantly high association of blackfoot disease with hyperpigmentation, keratosis, and skin cancer.

The risk of bladder cancer in Taiwan was increased with intake of arsenic from water of 10 $\mu\text{g}/\text{kg}/\text{day}$ (Chen et al., 1992). This increased risk has been confirmed in studies from Japan (Tsuda et al., 1995), Argentina (Hopenhayn-Rich et al., 1996), and Chile (Smith et al., 1998). Studies in U.S. populations exposed to arsenic in drinking water have not identified cancer increases (Morton et al., 1976; Southwick et al., 1981; Valentine et al., 1992).

These epidemiological associations have to some extent been replicated in animal experiments (Simeonova et al., 2000; Yamamoto et al., 1995). However, the mechanisms of arsenic carcinogenesis are not established, but may involve genetic effects (Goering et al., 1999) or perturbation of cellular signaling pathways (Simeonova et al., 2000).

Summary

Clearly, high intakes of inorganic arsenic are associated with various toxicities, including increased risks of several cancers with chronic exposure to high levels in drinking water. There is no evidence linking organic arsenic in food to any adverse effect, including cancer. Since there is no evidence available to define the mechanisms of arsenic carcinogenesis and no data to support a threshold, it is not possible to establish a health-based level of inorganic arsenic in drinking water and food. It should be noted that a recent report of the National Research Council recommended a downward revision from the current maximum contaminant level for arsenic in drinking water of 50 $\mu\text{g}/\text{L}$ (NRC, 1999). Because organic forms of arsenic are less toxic than inorganic forms, any increased health risk from intake of organic arsenic from food products such as fish is unlikely.

Intake Assessment

The highest concentrations of arsenic in food are found in marine products, but these are in the organic form, usually arsenobetaine, which is not toxic. Various sources of exposure to inorganic arsenic, as arsenates or arsenites, exist. Occupational exposure to inorganic forms of arsenic occurs primarily by inhalation. Arsenic in drinking water is predominantly the trivalent and pentavalent forms as salts (EPA, 1988). Arsenic is also being used in the treatment of leukemias (Konig et al., 1997; Look, 1998).

The median intake of arsenic by men and by women was approximately 2.0 to 2.9 $\mu\text{g}/\text{day}$ and 1.7 to 2.1 $\mu\text{g}/\text{day}$, respectively (Appendix Table E-2). Adams and coworkers (1994) reported lower intakes for adults (23 to 58 $\mu\text{g}/\text{day}$) from 1982 to 1991. The level of inorganic arsenic in water was about 2 $\mu\text{g}/\text{L}$ (ATSDR, 1998). The drinking water for about 98 percent of the U.S. population was below 10 $\mu\text{g}/\text{L}$ (Chappell et al., 1997). The U.S. Environmental Protection Agency (EPA) has a maximum contaminant level (MCL) of 50 $\mu\text{g}/\text{L}$ for water supplies in the United States (EPA, 1975). However, the agency recently proposed a much lower MCL of 5 $\mu\text{g}/\text{L}$ for arsenic in drinking water and is seeking comments on MCLs ranging from 3 to 20 $\mu\text{g}/\text{L}$ (EPA, 2000). The EPA expects to promulgate a new, lower MCL in the near future. The average arsenic content of mineral drinking water in European countries is 21 $\mu\text{g}/\text{L}$ (Zielhuis and Wibomo, 1984).

Risk Characterization

Although no UL was set for arsenic, there is no justification for adding arsenic to food and there may be a risk of adverse effects with consumption of organic arsenic in food or with intake of inorganic arsenic in water supplies at the current MCL of 50 $\mu\text{g}/\text{L}$ in the United States. Substantial numbers of individuals in North America, however, are exposed to arsenic levels exceeding the MCL (Chappell et al., 1997; Grantham and Jones, 1977; Kreiss et al., 1983). Inhalation exposure occurs in occupational settings such as smelters and chemical plants, where the predominant form of airborne arsenic is arsenic trioxide dust (ATSDR, 1998).

RESEARCH RECOMMENDATIONS FOR ARSENIC

- A better understanding of species differences in biotransformation of arsenic and toxicity.

- The role of arsenic in methyl metabolism and genetic expression; identification of a reliable indicator of arsenic status in humans.
- Because relatively low serum arsenic concentrations have been associated with vascular diseases and central nervous system injury, more systematic investigation of the possible role of arsenic in these disorders.

BORON

BACKGROUND INFORMATION

Function

Of the five minerals discussed in this chapter, boron has received the most extensive study of its possible nutritional importance for animals and humans. Still, the collective body of evidence has yet to establish a clear biological function for boron in humans. There is evidence that boron is required by vascular plants and some microorganisms. The only known boron-containing compounds in nature are organoboron complexes from plants, some of which may have antibiotic properties (Hunt, 1998; Nielsen, 1997). Principles of bioinorganic chemistry predict that boron, which is primarily in the form of boric acid, $B(OH)_3$, at physiological pH, binds to cis-diols, perhaps with some specificity, and forms condensation products that are moderately labile in aqueous solutions (da Silva and Williams, 1991). The latter could theoretically provide stability to diol-rich molecules such as polysaccharides or steroids. Boron can act as an inhibitor of activity for a wide variety of enzymes in vitro (Hunt, 1998). However, no boron-containing enzyme has been identified.

In higher animals, boron has not been shown to have a sufficiently definitive pattern of effects to establish a function. Embryonic defects related to boron depletion have been reported for zebra fish (Rowe and Eckhert, 1999), frogs (Fort et al., 1998, 1999), and trout (Eckhert, 1998), and they suggest a function for boron in reproduction and development. However, boron-related developmental defects have not been found consistently in rodent models (Lanoue et al., 1998, 1999). Physiological effects, including changes in blood glucose and triglyceride concentrations and abnormal calcitriol ($1,25(OH)_2D_3$) metabolism or function have been reported in boron-deficient chicks that have a concomitant vitamin D deficiency (Hunt, 1996). Higher insulin secretion from the pancreas of boron-deprived chicks has also been reported (Bakken, 1995). How-

ever, many of these studies found effects of boron only in the presence of secondary nutritional stressors, such as vitamin D deficiency.

Metabolism of vitamin D and estrogen, as measured by plasma metabolites, macromineral (especially calcium) metabolism, and immune function have been proposed as related to a function for boron in humans (Nielsen, 1998; Nielsen and Penland, 1999; Samman et al., 1998). Findings supporting these possible functions also have come from studies where another nutritional stressor was present or effects have not been consistently demonstrated. In one laboratory, several dietary boron deprivation studies in both rats and humans have consistently found an effect of boron intake on brain electrophysiology and, in humans, on performance of tasks measuring eye-hand coordination, attention, and short-term memory (Penland, 1998). However, these possible functions of boron have yet to be studied and confirmed by other laboratories.

Physiology of Absorption, Metabolism, and Excretion

Studies with animals and humans indicate that about 90 percent of boron is absorbed in the normal intake range (Hunt and Stoecker, 1996; Sutherland et al., 1998). Most dietary boron is hydrolyzed within the gut to yield $B(OH)_3$ which, as a neutral compound, is easily absorbed. The mechanism of boron absorption has not been studied, but a passive, nonmediated diffusion process involving $B(OH)_3$ is likely (da Silva and Williams, 1991). Some evidence for boron homeostasis exists. In a 42-day study in men with a boron intake average of 3.73 mg/day, urinary loss was 3.20 mg/day (86 percent of intake), whereas urinary boron loss was less when the boron intake was less than 3.20 mg/day and loss was more when the intake was more than that amount (Sutherland et al., 1998). In a study with postmenopausal women, 89 percent of boron from a low-boron diet (0.36 mg/day from food and 2.87 μ g/day from a supplement) was excreted in the urine and 3 percent in the feces (Hunt and Stoecker, 1996). Other metabolic studies do not support homeostatic control. For example, urinary excretion was 86 and 84 percent when boron intake was 2.2 and 10 mg/day, respectively (Samman et al., 1998).

Boron chemistry suggests it is transported in the blood as $B(OH)_3$. Specifically, because boron forms labile complexes in aqueous solution, transport is probably as free boric acid rather than a complex (da Silva and Williams, 1991). The blood boron concentration is dependent on dietary intake as primarily shown by animal studies (Price et al., 1998; Samman et al., 1998). This reflects the relatively

small boron pool that blood represents as well as efficient absorption and excretion. The excretory form of boron has not been studied. As a neutral molecule, blood borate should have high fractional renal clearance and easily enter the glomerular filtrate.

FINDINGS BY LIFE STAGE AND GENDER GROUP

There is evidence supporting a biological role of boron in some microorganisms. In higher animals, boron has been shown to have a role in reproduction and development. The collective body of evidence, however, has yet to establish a clear biological function for boron in humans. Therefore, neither an Estimated Average Requirement, Recommended Dietary Allowance, nor Adequate Intake was established for boron.

INTAKE OF BORON

Food Sources

Hunt and coworkers (1991) reported that the highest concentrations of boron were found in fruit-based beverages and products, tubers, and legumes. Depending on the geographic location, water could contribute a major portion of the dietary boron. Negligible or minimal amounts (less than 0.100 µg/g) were found in animal products, certain grain products, condiments, and confections. Similar findings were reported by Anderson and coworkers (1994). Meacham and Hunt (1998) reported that the ten foods with the highest concentration of boron were avocado, peanut butter, peanuts, prune and grape juice, chocolate powder, wine, pecans, and granola raisin and raisin bran cereals. Rainey and coworkers (1999), however, examined both the content and total food consumption (amount and frequency), reporting that the five major contributors of boron were coffee, milk, apples, dried beans, and potatoes, which collectively accounted for 27 percent of the dietary boron consumption. Although coffee and milk are low in boron, they were the top contributors due to the volumes consumed.

Dietary Intake

U.S. boron consumption was assessed by use of the Boron Nutrient Data Base linked to 2-day food records from respondents to the Third National Health and Nutrition Examination Survey (NHANES III) (Appendix Table C-12) and the Continuing Survey

of Food Intakes by Individuals (CFSII) (Appendix Table D-1). In NHANES III, the median consumption of boron ranged from 0.75 to 0.96 mg/day for school-aged children and from 0.87 to 1.35 mg/day for adults. Median consumption of boron by pregnant women was 1.05 mg/day in NHANES III and 1.08 mg/day in CFSII. The median consumption of boron by lactating women was 1.27 mg/day in CFSII.

Anderson (1992) reported that the mean boron concentration of human milk from lactating women up to 5 months postpartum was 0.27 µg/L. Based on a mean secretion of 0.78 L/day of milk (Chapter 2), the amount of boron secreted is 0.21 mg/day.

Intake from Supplements

Information from NHANES III on supplement intake of boron is given in Appendix Table C-13. The adult median boron intake from supplements was approximately 0.14 mg/day. Based on dietary intake data provided in Appendix Table C-12, the median intake of dietary and supplemental boron was approximately 1.0 to 1.5 mg/day for adults.

TOLERABLE UPPER INTAKE LEVELS

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects.

Hazard Identification

It should be noted that because some studies report doses of boron while others report doses of boric acid or borax, comparison of experiments is facilitated by expressing all doses as boron equivalents (e.g., boric acid dose \times 0.175; borax dose \times 0.113).

Adverse Effects

No data are available on adverse health effects from ingestion of large amounts of boron from food and water. According to case reports of poisoning incidents and accidental ingestions of boric acid and borax, these compounds exhibit low toxicity. Stokinger (1981) reported that the minimal lethal dose of boric acid from ingestion is 640 mg/kg/day. The potential lethal dose has been reported to be 15 to 20 g/day for adults and 3 to 6 g/day for infants; however, in an examination of 784 cases of boric acid ingestion, Litovitz and coworkers (1988) found minimal or no toxicity at these or higher intake levels. Initial symptoms include nausea, gastric discomfort, vomiting, and diarrhea. At higher doses, skin flushing, excitation, convulsions, depression, and vascular collapse have been reported.

Human Data. Most of the toxicity data on repeated administration of boron (as boric acid or borax) comes from studies in laboratory animals. However, from reports on the use of borates to treat epilepsy where doses between 1,000 mg/day of boric acid (2.5 mg/kg/day) to 25 g/day of boric tartrate (24.8 mg/kg/day) were administered chronically, toxicity was expressed as dermatitis, alopecia, anorexia, and indigestion (Culver and Hubbard, 1996). On the basis of their review of the human data in adults, Culver and Hubbard (1996) reported no adverse effects at chronic intakes of 2.5 mg/kg/day (about 1 g of boric acid). On the basis of nine cases involving infants (Gordon et al., 1973; O'Sullivan and Taylor, 1983), there does not appear to be an increased sensitivity of response to chronic exposure of boron compounds.

Genotoxicity. On the basis of existing data, genotoxicity is not an area of concern after exposure of humans to boron compounds (ATSDR, 1992; Dieter, 1994).

Reproductive and Developmental Effects in Animals. Although not observed in humans, animal studies have shown that high doses of borax or boric acid produce adverse effects in the testis and affect male fertility (IPCS, 1998). Also, adverse effects have been found in the developing fetus (Heindel et al., 1992; IPCS, 1998; Price et al., 1996a). Effects on the testis have been observed in three species—rats, mice, and dogs—after supplementation with boric acid or borates in feed or drinking water (Fail et al., 1990, 1991; Green et al., 1973; Ku et al., 1993; Lee et al., 1978; Weir and Fisher, 1972). The effects

tend to be similar in all three species and include inhibition of spermiation (release of spermatozoa into seminiferous tubule), loss of germ cells, changes in epididymal sperm morphology and caput sperm reserves, testicular atrophy, and decreased serum testosterone levels. Doses of 29 mg/kg/day in dogs and 58.5 mg/kg/day in rats have resulted in adverse reproductive effects. A comparison of the lowest-observed-adverse-effect levels (LOAELs) and no-observed-adverse-effect levels (NOAELs) for the key studies on reproduction is given in Table 13-1.

Pharmacokinetics. The pharmacokinetics of boron are very similar in animals and humans. There are several recent reviews of the available studies (Dourson et al., 1998; IPCS, 1998; Moore, 1997; Murray, 1998), and a summary of the key findings is presented here.

There is no evidence of boron accumulation in soft tissues of humans (Murray, 1998). In rats, boron increased more in bone than in plasma (Ku et al., 1991). Although methodological differences between studies preclude a clear-cut, cross-species comparison of blood boron concentrations in animals and humans at similar doses, IPCS (1998) reported a preliminary comparison between humans and rats after oral intakes of boron from diet or drinking water. Between 0.01 and 100 mg/kg/day, very similar blood levels were achieved at comparable intakes, further evidence that the kinetics of boron in humans and rats are alike.

Boron is rapidly excreted unchanged in the urine of humans and rodents regardless of the route of administration. In humans, the half-life for elimination was approximately 21 hours for both intravenously (Jansen et al., 1984a) and orally (Jansen et al., 1984b) administered boric acid. By using the data from Ku and coworkers (1991) and assuming first-order kinetics, the half-life in rats has been calculated in the range of 14 to 19 hours. As noted by Murray (1998) and Dourson and coworkers (1998), rats have mean glomerular filtration rates for boric acid three to four times that of humans, which could account for the small differences in blood (and, therefore, soft tissue) concentrations of boron noted by IPCS (1998).

Other Effects. Increased mortality was observed in mice fed dietary boric acid for periods of 13 weeks at boron levels of 563 mg/kg/day in females and 776 mg/kg/day in males (Dieter, 1994). Minimal to mild extramedullary hematopoiesis was noted at all doses for both sexes, and hyperkeratosis and hyperplasia of the forestomach also occurred at the highest doses for both sexes. Testicular atrophy or

TABLE 13-1 Ranking of Reproductive and Developmental Effects of Boron^a by Increasing Dose

Reference	Species/ Duration ^b	Dose (mg boron/ kg body weight/d) ^c	Effect ^d
Price et al., 1996b	SD rat/gd 0–20	9.6	NOAEL for developmental effects immediately preterm
Price et al., 1996b	SD rat/gd 0–20	12.9	NOAEL for developmental effects measured at weaning
Heindel et al., 1992	SD rat/gd 0–20	13.3 13.6	LOAEL for reduced fetal weight, increased rib malformations/variations
Weir and Fisher, 1972	Male SD rat/ multigeneration	17.5	NOAEL for male sterility, testicular atrophy
Fail et al., 1991	CD-1 mouse/ multigeneration	19.2	LOAEL for reduced sperm motility, reduced F ₂ pup weight
Price et al., 1996b	SD rat/gd 0–20	25.4	LOAEL for increased short rib XIII at weaning
Ku et al., 1993	Male SD rat/ 63 days	26	LOAEL for mild inhibited sperm release
Weir and Fisher, 1972	Male beagle dogs/ 2 years	29	Altered testis weight and histopathology LOAEL (reported NOAEL 8.8)
Price et al., 1996a	NZ white rabbits/ gd 6–19	21.9/43.7	NOAEL/LOAEL for decreased fetal body weight, increased fetal cardiovascular malformations and maternal toxicity
Heindel et al., 1992	CD-1 mouse/ gd 0–17	43 79	NOAEL for mouse developmental toxicity LOAEL for decreased fetal body weight
Ku et al., 1993	Male SD rat/ 63 days	52	LOAEL for testicular atrophy

^a Administered as boric acid.

^b SD = Sprague-Dawley rats, gd = gestational days, NZ = New Zealand.

^c Boric acid was converted to boron.

^d NOAEL = no-observed-adverse-effect level, LOAEL = lowest-observed-adverse-effect level.

SOURCE: IPCS (1998). Published here with permission of the World Health Organization.

degeneration was observed at doses of 141 mg/kg/day. These findings confirmed the earlier studies by Weir and Fisher (1972) in which rats fed 88 mg/kg/day of boron as borax or boric acid for 90 days developed testicular atrophy.

Summary

Based on the considerations of causality, relevance, and the quality and completeness of the database in animals, reproductive and developmental effects were selected as the critical endpoint on which to base a UL for adults. Because no data are available on adverse reproductive effects in humans from the consumption of large amounts of boron from food and water, animal data were utilized to estimate the UL. The following factors support the use of the laboratory animal studies listed in Table 13-1 to assess the developmental and reproductive risks from boron exposure in humans: (1) boric acid has been shown to cause developmental effects in four species of animals, (2) the toxicity of boric acid and borax correlates with their elemental boron content under physiological conditions, (3) the organs that are sensitive to the acute systemic effects of boron in humans and animals are similar, (4) the pattern of tissue distribution and excretion of boron is similar in animals and humans, and (5) the chronic effects of boron observed in mice, rats, and dogs and the effective doses are similar.

Dose-Response Assessment

Adults

Data Selection. In the absence of human data pertaining to a dose-response relationship, the animal data sets reporting developmental abnormalities are shown in Table 13-1. The studies showing developmental abnormalities at the lowest levels of intake are in dogs (Weir and Fisher, 1972) and rats (Price et al., 1996b). However, the study in dogs was not used directly in this risk assessment of boron due to problems in the design (few animals per treatment group and lack of information on food intake). The study of Price and coworkers (1996b) is considered the critical study to assess the risks to humans from exposure to boron.

Identification of a NOAEL and LOAEL. In the study by Price and coworkers (1996b), boric acid was fed to time-mated rats (60 per treatment group) from gestational days 0 to 20 at dosages of 3.3,

6.3, 9.6, 13.3, or 25 mg/kg/day. Maternal body weight did not differ among groups during gestation or lactation, and weight gain was not affected by the amount of boron in the diet. The most sensitive parameter of developmental toxicity was decreased fetal weights at gestational day 20, with significantly decreased fetal weights found only in the 13.3 and 25 mg/kg/day groups. Thus, a NOAEL of 9.6 mg/kg/day and a LOAEL of 13.3 mg/kg/day were reported.

In an earlier study in rats using a very similar experimental design, Heindel and coworkers (1992) reported an increase in fetal malformations with boric acid at dosages of 13.6, 28.5, and 57.7 mg/kg/day from gestational days 0 to 20. The most common malformations were enlargement of lateral ventricles in the brain, shortening of rib XIII, and wavy ribs. Although a LOAEL was found at the lowest dose tested (13.6 mg/kg/day), it is similar to the LOAEL of 13.3 mg/kg/day reported by Price and coworkers (1996b), a finding that provides additional support for the dose-response relationship for developmental toxicity as the critical effect.

Uncertainty Assessment. Five expert groups have assessed the risk to humans from boron using the NOAEL from Price and coworkers (1996b), and uncertainty factors (UFs) vary between 25 and 60 (Becking and Chen, 1998). There do not appear to be sufficient data to justify lowering the degree of uncertainty for extrapolating from experimental animals to humans from the 10 that is often used for nonessential chemicals. Thus, the usual value of 10 was selected. In view of the expected similarity in pharmacokinetics among humans, however, a UF of 3 was chosen for intraspecies variability. These two UFs are multiplied to yield a UF of 30.

Derivation of a UL. The NOAEL for developmental effects in rats is 9.6 mg/kg/day. The UL for boron is calculated by dividing the NOAEL of 9.6 mg/kg/day by the UF of 30, resulting in an UL of 0.32 mg/kg/day. This value was multiplied by the average of the reference body weights for adult women, 61 kg, from Chapter 1 (Table 1-1). The resulting UL for adults is rounded to 20 mg/day.

$$\text{UL} = \frac{\text{NOAEL}}{\text{UF}} = \frac{9.6 \text{ mg/kg/day}}{30} = 0.32 \text{ mg/kg/day} \times 61 \text{ kg} \cong 20 \text{ mg/day}$$

Boron UL Summary, Ages 19 Years and Older

UL for Adults

≥ 19 years 20 mg/day of boron

Other Life Stage Groups

Infants. For infants, the UL was judged not determinable because of insufficient data on adverse effects in this age group and concern about the infant's ability to handle excess amounts. To prevent high levels of intake, the only source of intake for infants should be from food and formula.

Children and Adolescents. There are no reports of boron toxicity in children and adolescents. Given the dearth of information, the UL values for children and adolescents are extrapolated from those established for adults. Thus, the adult UL of 20 mg/day of boron was adjusted for children and adolescents on the basis of relative body weight as described in Chapter 2 using reference weights from Chapter 1 (Table 1-1). Values have been rounded.

Pregnancy and Lactation. Because the UL is based on adverse reproductive effects in animals and because there are no reports of boron toxicity in lactating females, the UL for pregnant and lactating females is the same as that for the nonpregnant and nonlactating female.

Boron UL Summary, Ages 0 through 18 Years, Pregnancy, Lactation

UL for Infants

0–12 months **Not possible to establish; source of intake should be from food and formula only**

UL for Children

1–3 years **3 mg/day of boron**
4–8 years **6 mg/day of boron**
9–13 years **11 mg/day of boron**

UL for Adolescents

14–18 years **17 mg/day of boron**

UL for Pregnancy

14–18 years **17 mg/day of boron**
19–50 years **20 mg/day of boron**

UL for Lactation

14–18 years **17 mg/day of boron**
19–50 years **20 mg/day of boron**

Intake Assessment

Humans can be exposed to boron from consumption of food, dietary supplements, and drinking water from natural, municipal, or bottled sources. Airborne boron contributes very little to the daily exposure of the general population. For humans not taking supplements, diet is the major source of boron followed by the intake from drinking water.

The ninety-fifth percentile dietary intake of boron in the United States is approximately 2.3 mg/day for men, 1.6 to 2.0 mg/day for women, 2.0 mg/day for pregnant women (Appendix Table C-12), 2.7 mg/day for vegetarian males, and 4.2 mg/day for vegetarian females (Rainey et al., 1999). These dietary intakes are slightly higher than those estimated by Meacham and Hunt (1998). The average intake of supplemental boron at the ninety-fifth percentile is approximately 0.4 mg/day for adults (Appendix Table C-13). A consumption of 1 L/day of municipal drinking water in the United States contributes 0.005 to 2 mg/day (mean of 0.2 mg/day) of boron (EPA, 1987), and bottled water can contribute an average of 0.75 mg/day (Allen et al., 1989). Percutaneous absorption of boron from consumer products through intact skin has been shown to contribute very little to the total daily intake (Wester et al., 1998).

At the ninety-fifth percentile, intake of boron from the diet and supplements is approximately 2.8 mg/day. Adding to that a maximum intake from water of 2 mg/day gives a total intake of less than 5 mg/day boron at this percentile.

Risk Characterization

At the ninety-fifth percentile intake, no segment of the U.S. population has a total (dietary, water, and supplemental) intake of boron greater than 5 mg/day (Appendix Tables C-13 and D-1). Those taking body-building supplements could consume an additional 1.5 to 20 mg/day (Moore, 1997). Therefore this supplemental intake may exceed the UL of 20 mg/day.

RESEARCH RECOMMENDATIONS FOR BORON

- The relationship between dietary boron and vitamin D metabolism; specifically, does boron influence the half-life of functional vitamin D metabolites and calcium metabolism as it relates to bone mineralization?
- The possible influence of boron on estrogen metabolism and

function, particularly biological half-life, receptor-ligand interactions, and estrogen-inducible gene expression as related to bone mineral density.

- Studies of the possible role of boron in human neurophysiological and cognitive function that include delineation of a biochemical or other physiological basis for this function, in young as well as older populations.

NICKEL

BACKGROUND INFORMATION

Function

There have been no studies to determine the nutritional importance of nickel in humans, nor has a biochemical function been clearly demonstrated for nickel in higher animals or humans (Uthus and Seaborn, 1996). Nickel may serve as a cofactor or structural component of specific metalloenzymes of various functions, including hydrolysis and redox reactions and gene expression (Andrews et al., 1988; Kim et al., 1991; Lancaster, 1988; Przybyła et al., 1992). Nickel may also serve as a cofactor facilitating ferric iron absorption or metabolism (Nielsen, 1985). Nickel is an essential trace element in animals, as demonstrated by deficiency signs reported in several species. Rats deprived of nickel exhibit retarded growth, low hemoglobin concentrations (Schneegg and Kirchgessner, 1975), and impaired glucose metabolism (Nielsen, 1996). Nickel may interact with the vitamin B₁₂- and folic-acid dependent pathway of methionine synthesis from homocysteine (Uthus and Poellot, 1996).

Physiology of Absorption, Metabolism, and Excretion

The absorption of nickel is affected by the presence of certain foods and substances including milk, coffee, tea, orange juice, and ascorbic acid. Plasma ⁶²Ni was shown to peak between 1.5 and 2.5 hours after the ingestion of the stable isotope by four fasted, healthy men and women (Patriarca et al., 1997). The investigators reported no evidence that absorbed nickel was excreted via the gut. The percentage of nickel absorbed ranged from 29 to 40 percent. Urinary excretion of the ⁶²Ni dose ranged from 51 to 82 percent of the absorbed dose. Solomons and coworkers (1982) investigated absorption of nickel ingested with food and found that the presence of

food significantly decreased absorption. The absorption of dietary nickel is typically less than 10 percent.

Nickel is transported in blood bound primarily to albumin (Tabata and Sarkar, 1992). Although most tissues and organs do not significantly accumulate nickel, in humans the thyroid and adrenal glands have relatively high nickel concentrations (132 to 141 $\mu\text{g}/\text{kg}$ dry weight) (Rezuke et al., 1987). Most organs contain less than 50 μg of nickel/kg dry weight.

Because of the poor absorption of nickel, the majority of ingested nickel is excreted in the feces. The majority of absorbed nickel is excreted in the urine with minor amounts excreted in sweat and bile.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Nickel may serve as a cofactor or structural component of certain metalloenzymes and facilitate iron absorption or metabolism in microorganisms. No studies to determine the biological role of nickel in higher animals or humans have been reported. Therefore, neither an Estimated Average Requirement, Recommended Dietary Allowance, nor Adequate Intake was established for nickel.

INTAKE OF NICKEL

Food Sources

Major contributors to nickel intake are mixed dishes and soups (19 to 30 percent), grains and grain products (12 to 30 percent), vegetables (10 to 24 percent), legumes (3 to 16 percent), and desserts (4 to 18 percent) (Pennington and Jones, 1987). In food commodity groups, nickel concentrations are highest in nuts and legumes (128 and 55 $\mu\text{g}/100$ g, respectively), followed by sweeteners, including chocolate milk powder and chocolate candy. Of 234 foods analyzed, 66 percent had nickel concentrations less than 10 $\mu\text{g}/100$ g and 91 percent had concentrations less than 40 $\mu\text{g}/100$ g. Seven of these foods contained greater than 100 $\mu\text{g}/100$ g including nuts, legumes, and items with chocolate (Pennington and Jones, 1987). Major contributors of nickel to the Canadian diet include meat and poultry (37 percent), bakery goods and cereals (19 percent), soups (15 percent), and vegetables (11 percent) (Dabeka and McKenzie, 1995). Nielsen and Flyvholm (1983) suggested that nickel intakes in Denmark could reach over 900 $\mu\text{g}/\text{day}$ by the consumption of certain foods based on the nickel composition and level of consump-

tion of oatmeal, legumes (including soybeans), nuts, cocoa, and chocolate. Cooking foods in stainless steel utensils can increase the nickel content if the foods are acidic (Christensen and Moller, 1978).

Dietary Intake

Based on the Food and Drug Administration Total Diet Study of 1984, the mean nickel consumption of infants and young children was 69 to 90 $\mu\text{g}/\text{day}$ (Pennington and Jones, 1987). For adolescents, the median consumption was approximately 71 to 97 $\mu\text{g}/\text{day}$, and the median consumption for adults and the elderly was approximately 74 to 100 $\mu\text{g}/\text{day}$ and 80 to 97 $\mu\text{g}/\text{day}$, respectively (Appendix Table E-7). On the basis of a national survey conducted in five Canadian cities from 1986 to 1988, Dabeka and McKenzie (1995) reported that average nickel consumption for children was 190 to 251 $\mu\text{g}/\text{day}$; for adolescents, 248 to 378 $\mu\text{g}/\text{day}$; and for all adults, 207 to 406 $\mu\text{g}/\text{day}$.

At 38 days postpartum, the mean nickel concentration in human milk was reported to be 1.2 ng/mL (Casey and Neville, 1987). Based on an average secretion of 0.78 L/day (see Chapter 2), the mean secretion of nickel in human milk is approximately 1 $\mu\text{g}/\text{day}$. According to a report by Dabeka (1989), the average intake of nickel by 0- to 12-month-old Canadian infants was 38 $\mu\text{g}/\text{day}$, taking into account human milk as well as formula consumption.

Intake from Supplements

Information from the Third National Health and Nutrition Examination Survey on supplemental use of nickel is given in Appendix Table C-22. The median supplemental intake for adult men and women was approximately 5 $\mu\text{g}/\text{day}$. Therefore, adults consume approximately 79 to 105 $\mu\text{g}/\text{day}$ of nickel from diet and supplements.

TOLERABLE UPPER INTAKE LEVELS

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials

have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects. In addition, the UL is not meant to apply to individuals who are receiving nickel under medical supervision.

Hazard Identification

Adverse Effects

There is no evidence in humans of adverse effects associated with exposure to nickel through consumption of a normal diet. The UL derived here applies to excess nickel intake as soluble nickel salts.

Human Data. A few case reports have documented the acute effects of the ingestion of high doses of soluble nickel salts. Twenty workers who accidentally ingested 0.5 to 2.5 g of nickel as nickel sulfate and chloride hexahydrate in contaminated water developed nausea, abdominal pain, diarrhea, vomiting, and shortness of breath among other symptoms (Sunderman et al., 1988). Ten of these subjects were found to have altered hematological parameters. In one other case report, one subject who ingested approximately 50 µg/kg of nickel as nickel sulfate in water was reported to have developed transient hemianopsia at the time of peak serum concentrations (Sunderman et al., 1989). In persons with hypersensitivity to nickel, oral exposure has been reported to result in contact dermatitis-like symptoms (Gawkrodger et al., 1986).

Animal Data. In oral subchronic (ABC, 1988) and chronic (Ambrose et al., 1976) studies with rats, exposure to soluble nickel compounds has been associated with increased mortality, clinical signs of general systemic toxicity (e.g., lethargy, ataxia, irregular breathing, hypothermia, and salivation), decreased body weight gains, and changes in absolute and relative organ weights (kidney, liver, spleen, and heart). Fetotoxicity associated with oral exposure to nickel chloride and nickel sulfate has been reported in two separate two-generation studies (RTI, 1988; Smith et al., 1993) and in one three-generation study (Schroeder and Mitchner, 1971). Nickel salts also have been shown to interfere with the reproductive capacity of male rats (Hoey, 1966; Laskey and Phelps, 1991; Waltschewa et al., 1972).

Summary

On the basis of considerations of data quality, sensitivity of the

toxicological endpoint, and relevance to human dietary exposure, general systemic toxicity—in the form of decreased body weight gain reported in the subchronic and chronic rat studies (ABC, 1988; Ambrose et al., 1976)—was selected as the critical endpoint on which to base the derivation of the UL. Other data (e.g., hypersensitivity in humans and carcinogenic effects associated with inhalation exposure) were not considered relevant to human dietary exposure.

Dose-Response Assessment

Adults

Data Selection. A subchronic rat gavage study (ABC, 1988) and a chronic rat dietary study (Ambrose et al., 1976) were considered most suitable for establishing an UL for human dietary exposure to soluble nickel salts.

Identification of a No-Observed-Adverse-Effect Level (NOAEL) and a Lowest-Observed-Adverse-Effect Level (LOAEL). A NOAEL of 5 mg/kg/day was identified for both the 90-day subchronic gavage study (ABC, 1988) and the 2-year chronic dietary study (Ambrose et al., 1976) in rats. In both cases, the NOAEL was established on the basis of decreased body weight gains and signs of systemic toxicity at higher dose levels.

In the ABC (1988) study, groups of male and female CD rats were administered nickel chloride by water gavage at doses of 0, 5, 35, and 100 mg/kg/day for 3 months. On the basis of findings of decreased body weights, mortality, and clinical signs at higher doses, 5 mg/kg/day was concluded to be the NOAEL.

In the chronic study rats were administered nickel sulfate in the diet at doses of 0, 100, 1,000, or 2,500 ppm nickel (about 0, 5, 50, and 125 mg/kg/day) for a period of 2 years (Ambrose et al., 1976). Effects of treatment included reduced body weight gain in high-dose animals (125 mg/kg/day). Sporadic significant decreases in body weight gains were also recorded in the mid-dose group (50 mg/kg/day). Rats fed high- and mid-dose levels of nickel were reported to have significantly higher relative heart weights and lower relative liver weights. Although the study was suitable in design and conduct for use in establishing a UL for human dietary exposure to soluble nickel salts, poor survivorship in controls does raise some concern about its interpretability.

The results of three reproductive studies, one three-generation study (Schroeder and Mitchener, 1971) and two two-generation

studies (RTI, 1988; Smith et al., 1993), suggest potential for fetotoxicity after oral exposure to soluble nickel salts. The lowest LOAEL identified by Smith and coworkers (1993) was 1.3 mg/kg/day of nickel based on the total number of dead pups and the percentage of dead pups per litter. The Schroeder and Mitchener (1971) study concluded that exposure to nickel at a concentration of 5 mg/L, or about 0.4 mg/kg body weight/day (assuming 8 ml/100 g body weight), was associated with increased neonatal death; however, these conclusions were based on the results of only five non-randomized matings and therefore were not considered valid for use in determining a LOAEL for human dietary exposure to soluble nickel salts. In fact, all of the reproduction studies either were flawed or their interpretation was hampered by their statistical design and methodological and data-reporting limitations, as well as by inconsistencies in the reported dose-response relationships. As a result, these studies were not suitable for use in the establishment of a UL.

In summary, taken together, the oral subchronic and chronic rat studies support a NOAEL of 5 mg/kg body weight/day for soluble nickel salts. The selection of this NOAEL is in agreement with the NOAEL selected in the toxicological assessment of oral nickel exposure performed by the U.S. Environmental Protection Agency (EPA, 2000).

Uncertainty Assessment. When determining an uncertainty factor (UF) for nickel, several sources of uncertainty were selected to extrapolate from the NOAEL from the long-term rat study to the general population. The first UF of 10, which was used to extrapolate from the rat study to humans, incorporated uncertainties about the nature of the dose-response curve for nickel toxicity and uncertainties about the sensitivity of rats as compared with humans in respect to nickel toxicity. The second UF of 10 was to account for potential variation within the human population, especially in regard to the potential for nickel to induce hypersensitivity reactions in sensitive individuals. The third UF of 3 was introduced because of concerns raised by studies on reproductive effects, namely, that nickel may be a reproductive toxin at levels lower than the NOAEL observed for the chronic rat study. These three UFs were multiplied to yield the ultimate UF of 300 that would accommodate the general population including women who are pregnant or lactating.

Derivation of a UL. The NOAEL of 5 mg/kg body weight/day was divided by the UF of 300 to obtain a UL of 0.017 mg/kg body weight/day for adult humans. This figure was multiplied by the

average of the reference body weights for adult women, 61 kg, from Chapter 1 (Table 1-1). The resulting UL for adults is rounded down to 1.0 mg/day.

$$\text{UL} = \frac{\text{NOAEL}}{\text{UF}} = \frac{5 \text{ mg/kg/day}}{300} = 0.017 \text{ mg/kg/day} \times 61 \text{ kg} \cong 1.0 \text{ mg/day}$$

Nickel UL Summary, Ages 19 years and Older

UL for Adults

≥ 19 years 1.0 mg/day of soluble nickel salts

Other Life Stage Groups

Infants. For infants, the UL was judged not determinable because of the lack of data on adverse effects in this age group and concern about the infant's ability to handle excess amounts. To prevent high levels of intake, the only source of intake for infants should be from food and formula.

Children and Adolescents. There are no reports of nickel toxicity in children and adolescents. The UL values for children and adolescents were extrapolated from those established for adults. Thus, the adult UL of 1.0 mg/day of soluble nickel salts was adjusted for children and adolescents on the basis of relative body weight as described in Chapter 2 using reference weights from Chapter 1 (Table 1-1).

Pregnancy and Lactation. No data were found that could be used to identify a NOAEL or LOAEL and derive a UL for pregnant and lactating women. Therefore, the ULs for pregnant and lactating women are the same as for the nonpregnant and nonlactating women.

Nickel UL Summary, Ages 0 through 18 Years, Pregnancy, Lactation

UL for Infants

0–12 months Not possible to establish; source of intake should be from food and formula only

UL for Children

1–3 years	0.2 mg/day of soluble nickel salts
4–8 years	0.3 mg/day of soluble nickel salts
9–13 years	0.6 mg/day of soluble nickel salts

UL for Adolescents

14–18 years	1.0 mg/day of soluble nickel salts
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UL for Pregnancy

14–18 years	1.0 mg/day of soluble nickel salts
19–50 years	1.0 mg/day of soluble nickel salts

UL for Lactation

14–18 years	1.0 mg/day of soluble nickel salts
19–50 years	1.0 mg/day of soluble nickel salts

Special Considerations

Individuals with preexisting nickel hypersensitivity (from previous dermal exposure) and kidney dysfunction are distinctly susceptible to the adverse effects of excess nickel intake (Gawkrodger et al., 1986). These individuals may not be protected by the UL for nickel intake for the general population.

Intake Assessment

Based on the Food and Drug Administration Total Diet Study (Appendix Table E-7), 0.5 mg/day was the highest intake at the ninety-ninth percentile of nickel from food reported for any life stage and gender group; this was the reported intake for pregnant females. Nickel intake from supplements provided only 9.6 to 15 µg/day at the ninety-ninth percentile for all age and gender groups (Appendix Table C-22).

Risk Characterization

The risk of adverse effects resulting from excess intakes of nickel from food and supplements appears to be very low at the highest intakes noted above. Increased risks are likely to occur from environmental exposures or from the consumption of contaminated water.

RESEARCH RECOMMENDATIONS FOR NICKEL

- Identification and clear characterization of a biochemical function for nickel in humans; identification of a reliable indicator of nickel status for use in future studies of nickel deficiency.
- Further exploration of the possible role of nickel in vitamin B₁₂ and folate metabolism, including whether nickel nutrition should be a concern for pregnant women or people at risk for cardiovascular disease.

SILICON

BACKGROUND INFORMATION

Function

A functional role for silicon in humans has not yet been identified. In view of the distribution of silicon in the body, as well as the biochemical changes that occur in bone with a silicon deficiency, silicon appears to be involved with the formation of bone in chickens and rats (Carlisle, 1980a, 1980b, 1981; Schwarz and Milne, 1972). Silicon contributes to prolylhydroxylase activity, which is important for collagen formation (Carlisle, 1984). Chicks fed a silicon-deficient diet exhibited structural abnormalities of the skull and long-bone (Carlisle, 1984). Rats deprived of silicon showed decreased bone hydroxyproline and alkaline and acid phosphatases (Seaborn and Nielsen, 1993, 1994). Silicon has been suggested to have a preventive role in atherogenesis (Mancinella, 1991).

Physiology of Absorption, Metabolism, and Excretion

Findings that as much as 50 percent of ingested silicon is excreted in the urine (Kelsay et al., 1979) suggest that some dietary forms of silicon are well absorbed. Silicon in blood exists almost entirely as silicic acid and is not bound to proteins. Various connective tissues including the aorta, trachea, bone, tendons, and skin contain most of the silicon present in the body (Carlisle, 1984). Significantly higher serum silicon concentrations were seen in patients with chronic renal failure (46 $\mu\text{mol/L}$) compared to controls (21 $\mu\text{mol/L}$) (Dobbie and Smith, 1986).

In a study by Popplewell et al. (1998), 48 hours after ingestion of ³²Si, 36 percent of the dose was excreted in the urine and elimination appeared to be complete. This study, however, did not elimi-

nate the possibility of longer-term retention of additional ^{32}Si . Goldwater (1936) reported daily silicon excretion levels for five subjects averaging 10 mg/day and ranging from 5 to 17 mg/day. Kelsay and coworkers (1979) studied 11 men fed low- and high-fiber diets and found their urinary silicon excretion to be 12 and 16 mg/day, respectively, amounts which were not significantly different.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Silicon appears to be involved in the formation of collagen and bone in animals. A biological role of silicon in humans has not yet been identified. Therefore, neither an Estimated Average Requirement, Recommended Dietary Allowance, nor Adequate Intake was established for silicon.

INTAKE OF SILICON

Food Sources

Concentrations of silicon are higher in plant-based foods than in animal-derived food products. Based on the Food and Drug Administration Total Diet Study, beverages, including beer, coffee, and water, are the major contributors of silicon (55 percent), followed by grains and grain products (14 percent), and vegetables (8 percent) (Pennington, 1991). Refining reduces the silicon content in foods. Silicate additives that have been increasingly used as anti-foaming and anticaking agents can raise the silicon content in foods; however, the bioavailability of these additives is low.

Dietary Intake

Based on the Total Diet Study, the mean intakes of silicon in adult men and women were 40 and 19 mg/day, respectively (Pennington, 1991). Appendix Table E-8 indicates that the daily median intakes of silicon for adult men and women ranged from approximately 14 to 21 mg/day. Kelsay and coworkers (1979) found intakes of 46 mg/day from a high-fiber diet and 21 mg/day from a low-fiber diet.

The mean concentration of silicon in human milk was reported to be 0.47 mg/L in women up to 5 months postpartum (Anderson, 1992). Based on the mean secretion of 0.78 L of human milk per day (Chapter 2), the mean intake of silicon by infants receiving human milk is approximately 0.37 mg/day.

Intake from Supplements

Information from the Third National Health and Nutrition Examination Survey on supplement use of silicon is provided in Appendix Table C-23. The median intake of supplemental silicon by adults was approximately 2 mg/day.

TOLERABLE UPPER INTAKE LEVELS

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects.

Hazard Identification

There is no evidence that silicon that occurs naturally in food and water produces adverse health effects. Limited reports indicate that magnesium trisilicate (6.5 mg of elemental silicon per tablet) when used as an antacid in large amounts for long periods (i.e., several years) may be associated with the development of urolithiasis due to the formation, *in vivo*, of silicon-containing stones (Haddad and Kouyoumdjian, 1986). Less than 30 cases of urolithiasis reported to be associated with intake of silicates (in the form of antacids) could be found even though antacids containing silicon have been sold since the 1930s.

Takizawa and coworkers (1988) examined the carcinogenicity of amorphous silica (SiO_2) given by the oral route to rats and mice for approximately 2 years. There was no evidence that orally administered silica induced tumors.

Dose-Response Assessment

There are no adequate data demonstrating a no-observed-adverse-effect level (NOAEL) for silicon. Apart from scattered reports of silicate-induced urolithiasis, said to be associated with antacids, the limited toxicity data on silicon suggest that typical levels of intake

have no risk of inducing adverse effects for the general population. Due to lack of data indicating adverse effects of silicon, it is not possible to establish a UL.

RESEARCH RECOMMENDATIONS FOR SILICON

- The physiological role of silicon and how this role relates to human health.
- The possible role of silicon in atherosclerosis and hypertension, several bone disorders, Alzheimer's disease, and other conditions common to the elderly because of the prevalence and cost of these disorders.
- The determination of a reliable indicator of silicon status.

VANADIUM

BACKGROUND INFORMATION

Function

A functional role for vanadium in higher animals and humans has not yet been identified. Vanadium mimics insulin and stimulates cell proliferation and differentiation (Heyliger et al., 1985; Nielsen and Uthus, 1990). Vanadium inhibits various ATPases, phosphatases, and phosphoryl-transfer enzymes (Nielsen, 1985). The response of thyroid peroxidase to changing dietary iodine concentrations has been shown to be altered in vanadium-deprived rats (Uthus and Nielsen, 1990). Vanadium-deprived goats show elevated abortion rates and decreased milk production (Anke et al., 1989). In vitro, vanadium in the form of vanadate regulates hormone, glucose, and lipid metabolism; however, vanadium most probably exists in the vanadyl form in vivo (Rehder, 1991).

Vanadium in the forms of vanadyl sulfate (100 mg/day) and sodium metavanadate (125 mg/day) has been used as a supplement for diabetic patients (Boden et al., 1996; Cohen et al., 1995; Goldfine et al., 1995). Although insulin requirements were decreased in patients with Type I diabetes, the doses of vanadium used in the supplements were about 100 times the usual intakes (Pennington and Jones, 1987), and they greatly exceed the Tolerable Upper Intake Level (UL) for vanadium.

Physiology of Absorption, Metabolism, and Excretion

The absorption of ingested vanadium is less than 5 percent, and therefore most ingested vanadium is found in the feces. Absorbed vanadate is converted to the vanadyl cation, which can complex with ferritin and transferrin in plasma and body fluids (Harris et al., 1984; Sabbioni et al., 1978). Highest concentrations of vanadium are found in the liver, kidney, and bone. However, very little of the absorbed vanadium is retained in the body. Patterson and coworkers (1986) investigated vanadium metabolism in sheep and suggested a compartmental model with certain tissues constituting a “slow turnover” pool where the turnover times for vanadium might exceed 400 days. Other tissues were suggested to constitute a “fast turnover” pool with vanadium residency of about 100 hours.

FINDINGS BY LIFE STAGE AND GENDER GROUP

In laboratory animals, vanadium mimics insulin (diminishes hyperglycemia and improves insulin secretion) and inhibits the activity of various enzymes. A deficiency of vanadium results in increased abortion rates. A biological role of vanadium in humans has not yet been identified. Therefore, neither an Estimated Average Requirement, Recommended Dietary Allowance, nor Adequate Intake was determined for vanadium.

INTAKE OF VANADIUM

Food Sources

Foods rich in vanadium include mushrooms, shellfish, black pepper, parsley, dill seed, and certain prepared foods. Myron and coworkers (1977) reported that processed foods contained more vanadium than nonprocessed foods. Byrne and Kosta (1978) also suggested that beer and wine may contribute an appreciable amount of vanadium to the diet. Commodity groups highest in vanadium are grains and grain products, sweeteners, and infant cereals. Analysis of data from the 1984 Food and Drug Administration Total Diet Study (Pennington and Jones, 1987) showed grains and grain products contributed 13 to 30 percent of the vanadium in adult diets. Beverages were also an important source for adults and elderly men (26 to 57 percent). This study also reported that 88 percent of the foods consumed had concentrations less than 2 µg/100 g. Canned apple

juice and cereals were the major contributors of vanadium to the diets of infants and toddlers.

Dietary Intake

Pennington and Jones (1987) reported that vanadium intake ranged from 6.5 to 11 $\mu\text{g}/\text{day}$ for infants, children, and adolescents. The intake of vanadium for adults and the elderly ranged from 6 to 18 $\mu\text{g}/\text{day}$.

Intake from Supplements

Information from the Third National Health and Nutrition Examination Survey on supplement use of vanadium is provided in Appendix Table C-24. The median intake of supplement vanadium by adults was approximately 9 $\mu\text{g}/\text{day}$. Vanadium in the forms of vanadyl sulfate (100 mg/day) and sodium metavanadate (125 mg/day) has been used as a supplement for diabetic patients (Boden et al., 1996; Cohen et al., 1995; Goldfine et al., 1995). Although insulin requirements were decreased in patients with Type I diabetes, the doses of vanadium used in the supplements were about 100 times the usual intakes (Pennington and Jones, 1987), and they greatly exceed the Tolerable Upper Intake Level (UL) for vanadium.

TOLERABLE UPPER INTAKE LEVELS

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects. In addition, the UL is not meant to apply to individuals who are receiving vanadium under medical supervision.

Hazard Identification

There is no evidence of adverse effects associated with vanadium intake from food, which is the major source of exposure to vanadium for the general population (Barceloux, 1999). There are data on

adverse effects associated with vanadium intake from supplements and drinking water. Because the forms found in food and supplements are the same (i.e., tetravalent or vanadyl [VO_2^+] and pentavalent or vanadate [VO_3^-] forms), the UL value will apply to total vanadium intake from food, water, and supplements.

Most vanadium toxicity reports involve industrial exposure to high levels of airborne vanadium. The most toxic vanadium compound is vanadium pentoxide, but because vanadium pentoxide is not a normal constituent of food, supplements, or drinking water, it will not be considered in this review.

Weight training athletes use up to 60 mg/day of vanadyl sulfate supplements (or 18.6 mg of elemental vanadium) to improve performance (Barceloux, 1999). Furthermore, because vanadium may become useful in future treatment of diabetes, there is increased concern about its long-term toxicity.

Adverse Effects

Acute Toxicity. Acute vanadium poisoning has not been observed in humans. Acute poisoning from sodium vanadate in rats causes desquamative enteritis, mild liver congestion with fatty changes, and slight parenchymal degeneration of the renal convoluted tubules (Daniel and Lillie, 1938). In mice, a subcutaneous dose of 20 mg/kg of ammonium metavanadate produced acute tubular necrosis by 6 to 7 hours postinjection (Wei et al., 1982).

Renal Toxicity. Evidence of renal toxicity associated with high vanadium intake in humans was not found. There is evidence of kidney effects in animals (Table 13-2). Domingo and coworkers (1985) found histopathological lesions of the kidney and increased plasma urea and uric acid concentrations in rats exposed to 50 $\mu\text{g}/\text{mL}$ in drinking water for 3 months. This finding suggests possible alterations in renal function. In a second study, Domingo and coworkers (1991) evaluated the toxicity of sodium metavanadate (0.15 mg/mL), sodium orthovanadate (0.23 mg/mL), and vanadyl sulfate pentahydrate (0.31 mg/mL) solutions given to diabetic rats for 28 days. In the vanadium-treated animals, they observed decreased weight gain and increased serum concentrations of urea and creatinine, as well as some deaths. A histopathological investigation was not performed.

Boscolo and coworkers (1994) reported that the lumen of the proximal tubules was narrowed and contained amorphous material in rats fed 40 $\mu\text{g}/\text{mL}$ of sodium metavanadate in drinking water for

TABLE 13-2 Animal Data on Vanadium-Induced Renal Toxicity, by Increasing Dose

Study	Species	Form	Dose (µg/mL)	Dose (mg/kg/d)	Duration
Wei et al., 1982	Mouse	Vanadate	ND ^a	20	6–7 hr
Boscolo et al., 1994	Rat	Vanadate	1	ND	≈ 7 mo
		Vanadate	10	ND	≈ 7 mo
		Vanadate	40	ND	≈ 6 mo
Domingo et al., 1985	Rat	Vanadate	5	0.8	3 mo
		Vanadate	10	1.5	3 mo
		Vanadate	50	7.7 ^b	3 mo
Domingo et al., 1991	Rat	Vanadate	ND	6.1	1 mo
		Vanadate	ND	15.6	1 mo
		Vanadyl	ND	22.7	1 mo

^a ND = not determined.

^b 7.7 mg/kg/d was calculated by using average weight of growing rats of 271 g and

6 or 7 months. Hydropic degeneration was also seen in some proximal and distal tubules and the loop of Henle. Because water intakes were not provided, this study could not be used to derive a dose. Acute tubular necrosis was observed in mice fed 20 mg/kg/day of ammonium metavanadate (Wei et al., 1982). The effect of supplemental vanadium intake on renal function needs further careful study.

Gastrointestinal Effects. There is human evidence of mild gastrointestinal effects (abdominal cramps, loose stool) primarily in patients with diabetes and animal evidence of more severe gastrointestinal effects (diarrhea, death) after ingestion of vanadium compounds (Boden et al., 1996; Dimond et al., 1963; Franke and Moxon, 1937; Goldfine et al., 1995). The human data are summarized in Table 13-3.

Hematological Effects. Vanadium compounds may cause anemia and changes in the leukocyte system. Animal studies of hemolytic activity of vanadium salts have conflicting results (Dai and McNeill, 1994; Dai et al., 1995; Hogan, 1990; Zaporowska and Wasilewski, 1992;

/kg/d)	Duration	Results
	6–7 hr	Acute tubular necrosis
	≈ 7 mo	No effects
	≈ 7 mo	Effects on kidney morphology (less evident)
	≈ 6 mo	Effects on kidney morphology
	3 mo	No effects
	3 mo	Vanadium detected in kidneys
	3 mo	Increased uric acid and urea; vanadium detected in kidneys
	1 mo	Increased serum urea and creatinine
	1 mo	Increased serum urea, but not creatinine
	1 mo	Increased serum urea and creatinine

average drinking water consumption of 42 mL/day. $50 \mu\text{g}/\text{mL} \times 42 \text{ mL}/\text{d} \times 1/0.27/\text{kg}$ body weight $\times 1 \text{ mg}/1,000 \mu\text{g} = 7.7 \text{ mg}/\text{kg}/\text{day}$.

Zaporowska et al., 1993). Fawcett and coworkers (1997) showed no effects of oral vanadyl sulfate (0.5 mg/kg body weight/day) on hematological indexes, blood viscosity, and biochemistry in a 12-week, double-blind, placebo-controlled trial in 31 athletes.

Cardiovascular Effects. Exposure to vanadate induced an increase in blood pressure and heart rate in rats (Carmignani et al., 1991; Steffen et al., 1981). Boscolo and coworkers (1994) showed an increase in arterial blood pressure following chronic exposure of rats to 1, 10, and 40 $\mu\text{g}/\text{mL}$ of vanadium for 6 or 7 months. These changes were not dose-dependent.

Reproductive Effects. No evidence of reproductive abnormalities after ingestion in humans was found. Two animal studies evaluating the reproductive toxicity of vanadium have been reported: in one, Llobet and coworkers (1993) observed that at 60 and 80 mg/kg body weight/day, a significant decrease in pregnancy rate occurred; in the other, Domingo and coworkers (1986) found no effects on fertility or reproduction in rats gavaged up to 20 mg/kg body weight/day with sodium metavanadate.

TABLE 13-3 Human Data on Vanadium-Induced Gastrointestinal Effect, by Increasing Dose

Study ^a	Subjects	Form	Dose ^b (mg V/d)	Dose ^c (mg/kg/d)	Duration
Dimond et al., 1963	6 adults	Vanadyl	5	0.07	6–10 wk
			10	0.15	
			15	0.2	
			20	0.3	
Cohen et al., 1995	6 adults	Vanadyl	31	0.5	3 wk
Boden et al., 1996	8 adults	Vanadyl	31	0.5	4 wk
Goldfine et al., 1995	10 adults	Vanadate	52	0.8	2 wk

^a Dimond was uncontrolled; Cohen, Boden, and Goldfine were noninsulin-dependent diabetics.

^b mg vanadium (V)/d was calculated as follows: For Dimond, mg V/d = 51 (molecular weight of V) ÷ 250 (molecular weight of ammonium vanadyl tartrate [i.e., 150 for tartaric acid minus 1 for H = 149 for tartrate + 101 for ammonium vanadyl, i.e., 117 for ammonium vanadate minus 16 for oxygen = 250]) = 0.20 × 25 mg/d (amount of

Other Adverse Effects. Other adverse effects associated with vanadium intake in humans include green tongue, fatigue, lethargy, and focal neurological lesions (Barceloux, 1999). These effects, however, have not been consistently observed or dose-related. No studies were found evaluating the genotoxicity in humans or animals after ingestion of vanadium, and no evidence was found showing carcinogenicity of vanadium compounds in animals or humans. The U.S. Environmental Protection Agency recently set an oral reference dose of 0.009 mg/kg/day for vanadium pentoxide based on decreased hair cystine content. This finding is from a chronic oral rat study described by Stokinger (1981). Because it is not clear that reduced hair cystine is an adverse effect, data on reduced hair cystine were judged not relevant to the derivation of a UL for elemental vanadium.

Summary

On the basis of the quality and completeness of the database and the strength of the causal association, renal toxicity was selected as the critical adverse effect on which to base a UL. The data on other

mg/kg/d) ^c	Duration	Result
	6–10 wk	Cramping, diarrhea, black loose stools \geq 20 mg/d
	3 wk	Mild gastrointestinal effects
	4 wk	Mild gastrointestinal effects
	2 wk	Mild gastrointestinal effects

compound given by Dimond) = 5 mg/d. For Cohen and Boden, mg V/d = $51 \div 163$ (molecular weight of vanadyl sulfate) = 0.31 \times 100 mg/d (amount of compound given by Cohen and Boden) = 31 mg/d. For Goldfine, mg V/day = $51 \div 122$ (molecular weight for NaVO₃) = 0.42 \times 125 (amount of compound given by Goldfine) = 52 mg/d. ^cBody weight used was the average of the reference weights for adult men and women (76 and 61 kg, respectively).

effects such as hematological, cardiovascular, or reproductive effects are not consistent. While gastrointestinal effects appear to occur at lower doses in humans, the specificity of the observed effects and the dose-response relationship are not as clearly defined as the histopathological lesions and adverse kidney effects demonstrated in animals. While kidney effects have not been demonstrated in humans, excess vanadium has been shown in rats to accumulate in kidneys (Oster et al., 1993), and the evidence in different species (i.e., mice and rats) further supports a possible risk in humans. Because of the widespread use of high-dose (60 mg/day) supplemental vanadium by athletes and other subgroups (e.g., borderline diabetics) that are considered part of the apparently healthy general population (Barceloux, 1999), further research on vanadium toxicity is needed.

Dose-Response Assessment

Adults

Data Selection. The data in laboratory rats involving subchronic to chronic durations of intake were used to derive a UL. Studies that

provided doses in units of concentration but provided no information on the body weights of the rats or the amount of water consumed were not used.

Identification of a No-Observed-Adverse-Effects Level (NOAEL) or Lowest-Observed-Adverse-Effects Level (LOAEL). A NOAEL of 0.8 mg/kg body weight/day and a LOAEL of 7.7 mg/kg body weight/day were determined on the basis of the results of Domingo and coworkers (1985). Vanadium could not be detected in the kidneys of animals receiving 5 µg/mL (or 0.8 mg/kg/day) (Table 13-2). Also, plasma urea, uric acid, and creatinine concentrations were within the normal range in this treatment group (Domingo et al., 1985). However, the study does not indicate whether there were kidney lesions at this level; therefore, whether this is a true NOAEL value for this study is uncertain. The same can be said for the treatment group given 10 µg/mL (or 1.5 mg/kg/day). The study does not provide enough detail about the findings at this dose level to ascertain whether it is a NOAEL or LOAEL.

The value of 7.7 mg/kg/day is the best estimate of a LOAEL from this data set. At this dose, there were evident lesions of the kidney and small, but significant, increases in plasma urea and uric acid. Furthermore, this LOAEL appears to be consistent with other studies (Boscolo et al., 1994; Domingo et al., 1991). Boscolo and coworkers (1994) failed to provide information on intakes (mg/kg/day), and therefore the study was judged not useful for deriving a UL. Nevertheless, both Domingo and coworkers (1991) and Boscolo and coworkers (1994) showed a similar dose-response relationship. The study by Domingo and coworkers (1991) in diabetic rats provides results that are fairly consistent with their earlier study (Domingo et al., 1985). Although Domingo and coworkers (1991) tested different compounds of vanadium and used a shorter duration, they observed increased serum urea and creatinine concentrations at similar doses (6.1 and 22.7 mg/kg/day).

Uncertainty Assessment. In determining an uncertainty factor (UF) for vanadium, several sources of uncertainty were considered and combined into the final UF. The severity of kidney lesions justifies a UF higher than 1, and so a UF of 3 was selected to extrapolate from the LOAEL to the NOAEL. A UF of 10 was selected to extrapolate from laboratory animals to humans because no human and little animal data were available to use in the dose-response assessment. Another UF of 10 was selected for intraspecies variability. The three

UFs are multiplied to yield an overall UF of 300 to extrapolate from the LOAEL in animals to derive a UL in humans.

Derivation of a UL. The LOAEL of 7.7 mg/kg/day was divided by a UF of 300 to obtain a UL of 0.026 mg/kg/day or 26 µg/kg/day for adult humans. This value was rounded and multiplied by the average of the reference body weights for adult men and women, 68.5 kg, from Chapter 1 (Table 1-1). The resulting UL for adults is 1.78 mg/day (which was rounded to 1.8 mg/day).

$$\text{UL} = \frac{\text{LOAEL}}{\text{UF}} = \frac{7.7 \text{ mg/kg/day}}{300} = 26 \text{ } \mu\text{g/kg/day} \times 68.5 \text{ kg} \cong 1.8 \text{ mg/day}$$

Vanadium UL Summary, Ages 19 Years and Older

UL for Adults

≥ 19 years 1.8 mg/day of elemental vanadium

Other Life Stage Groups

Given the severity of the critical effect for vanadium in adults, the lack of data on vanadium toxicity in other more sensitive life stage groups is of particular concern. Due to this lack of data, it was not possible to determine ULs for pregnant and lactating women, children, and infants. These individuals should be particularly cautious about consuming vanadium supplements. As indicated above, more research is needed on the renal effects of vanadium intake, particularly in these sensitive subgroups.

Vanadium UL Summary, Ages 0 through 18 Years, Pregnancy, Lactation

UL for Infants

0–12 months Not possible to establish; source of intake should be from food and formula only

UL for Children

1–3 years Not possible to establish; source of intake should be from food only

4–8 years Not possible to establish; source of intake should be from food only

9–13 years Not possible to establish; source of intake should be from food only

UL for Adolescents

14–18 years **Not possible to establish; source of intake should be from food only**

UL for Pregnancy

14–18 years **Not possible to establish; source of intake should be from food only**

19–50 years **Not possible to establish; source of intake should be from food only**

UL for Lactation

14–18 years **Not possible to establish; source of intake should be from food only**

19–50 years **Not possible to establish; source of intake should be from food only**

Special Considerations

A review of the literature revealed no special subpopulations that are distinctly susceptible to the adverse effects of high vanadium intake.

Intake Assessment

Although percentile data are not available for dietary vanadium intakes from U.S. surveys, the highest mean intake of vanadium reported for the U.S. population was 18 µg/day (Pennington and Jones, 1987). The average intake of supplemental vanadium at the ninety-ninth percentile by adults was 20 µg/day, which is significantly lower than the adult UL for vanadium.

Risk Characterization

The risk of adverse effects resulting from excess intake of vanadium from food is very unlikely. Because of the high doses of vanadium present in some supplements, increased risks are likely to result from the chronic consumption of supplements containing large doses of vanadium. Currently, doses of vanadium greater than the UL are being tested for their benefits in treating diabetics. The UL is not meant to apply to individuals who are being treated with vanadium under close medical supervision.

RESEARCH RECOMMENDATIONS FOR VANADIUM

- Determination of the biochemical role of vanadium in both higher animals and humans and a reliable status indicator of vanadium for further work in humans.
- The efficacy and safety of the use of vanadium as a nutritional supplement.

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