Deliberations and Evaluations of the Approaches, Endpoints and Paradigms for Boron, Chromium and Fluoride Dietary Recommendations\textsuperscript{1,2}

\textbf{ABSTRACT} The 10th edition (1989) of the Recommended Dietary Allowances provided estimated safe and adequate daily dietary intakes (ESADDI) for chromium and fluoride and summarized the substantial evidence for boron essentiality in animals. New approaches, endpoints and paradigms to use to formulate dietary guidance for these elements were reviewed recently by a discussion group and deliberations of the group are summarized to facilitate future discussions on dietary guidance for these elements.

The status category, estimated safe and adequate daily dietary intake (ESADDI), was created (NRC 1980) for nutrients with databases insufficient for developing approaches, endpoints and paradigms to use to formulate dietary guidance for these elements were reviewed recently by a discussion group and deliberations of the group are summarized to facilitate future discussions on dietary guidance for these elements.

The 10th edition of the Recommended Dietary Allowances (RDA)\textsuperscript{5} (NRC 1989) provided estimated safe and adequate daily dietary intakes (ESADDI) for chromium and fluoride and summarized the substantial evidence for boron essentiality in animals. New approaches, endpoints and paradigms to use to formulate dietary guidance for these elements were reviewed recently by a discussion group and deliberations of the group are summarized to facilitate future discussions on dietary guidance for these elements.

The status category, estimated safe and adequate daily dietary intake (ESADDI), was created (NRC 1980) for nutrients with databases insufficient for developing dietary guidance.
an RDA, but for which potentially toxic upper intakes were known. There is a need to replace the ESADDI category because of ambiguities in interpretation of values provided. For example, the term “safe” as used in the ESADDI can be misinterpreted as the upper safe limit of intake. Ambiguities are best eliminated by renaming the category; “provisional RDA” could be a term for a category that provides dietary guidance but acknowledges limitations of the data used to set it. A provisional RDA would be defined for a dietary substance that meets criteria set for one of two classes of nutrients: class 1, clear evidence of essentiality but uncertain or limited quantitative data or endpoints to use for defining dietary requirements; and class 2, strong evidence of essentiality and clear nutritional benefit based on reasonably certain quantitative data, but lack of clear information on function or endpoints to use for defining dietary requirements. Specific approaches for assigning provisional RDAs for each of the three elements, boron, chromium and fluoride, are discussed below.

**BORON**

**Current RDA status of boron**

The text accompanying the 10th edition of the Recommended Dietary Allowances (NRC 1989) noted that “boron has long been known to be essential for the growth of most plants.” “There is substantial evidence to establish the essentiality of [boron] in animals . . . . Boron deficiency has been reported in studies in rats, chickens, and humans. Boron appears to affect calcium and magnesium metabolism and may be needed for membrane function. Boron deficiency signs may be related to the level of vitamin D and possibly other nutrients in the diet.” The text also noted that “many dietary constituents are either essential for, or complementary to, the proper utilization of calcium, including . . . boron.” “Evidence for a requirement in laboratory animals has been presented for [boron] but . . . the requirement has not been quantified. Deficiency in humans has not been established for [boron]. Hence, there are no data from which a human requirement could be estimated and no provisional allowance can be given.”

As described in the 10th edition of the Recommended Dietary Allowances (NRC 1989), the RDAs are based in principle on one or more of six kinds of evidence. It is now possible to suggest approaches, endpoints and paradigms for establishing a provisional allowance for boron because new data pertinent to four of these kinds of evidence are available: boron intakes of apparently healthy people from their food supply, boron balance studies that measure nutrient status in relation to boron intake, adequacy of molecular function in relation to boron intake and human boron depletion/repletion studies.

**Boron intakes of healthy people**

Good estimates of boron intake are now available because of improvements in boron analytical technology. Recent analyses of food and personal care products (Anderson et al. 1994, Hunt et al. 1991, Iyengar et al. 1990) indicate that usual adult human dietary boron consumption in the United States is in the range of 1–2 mg [0.092–0.185 mmol]/d, not 10–25 mg [0.925–2.31 mmol]/d as calculated earlier [Ploquin 1967]. However, all recently calculated intakes are probably less than actual intakes by more than 10% because the calculations were based on the Food and Drug Administration Total Diet Study (TDS) [Pennington 1983]. Diets constructed from the TDS food lists for U.S. men and women aged 25–30 y do not provide sufficient energy for weight maintenance despite energy adjustments with sucrose, followed by a 10% increase in all foods [Hunt et al. 1992]. Because boron is present in most all plant food sources and this boron apparently is well absorbed, “background” boron concentrations occur in human blood and tissue [Restuccio et al. 1992]. The main sources of boron in the diet are drinking water [with major fluctuations between geographical locations], fruits, vegetables, legumes and nuts [Varo et al. 1980].

**Boron status in relation to boron intake**

Boron balance is influenced by at least three processes: gut absorption, blood transport and urinary excretion. Certain aspects of these processes are relevant to assessments of boron balance as an approach to establishing an RDA for boron.

**Boron absorption and excretion**

The bioavailability of boron in water [normally present as undissociated boric acid] or boron in a readily soluble inorganic form apparently is very high. For example, in a recent metabolic study (Hunt et al. 1994), postmenopausal women, fed a low boron diet [0.36 mg [0.033 mmol] B/d] and supplemented with 2.87 mg [0.265 mmol] B/d [as sodium tetraborate], excreted 89% of their total daily boron intake in the urine and only 3% [within analytical error] of the intake in the feces. The bioavailability of boron in foods is also apparently very high. Urinary excretion data collected from rats indicated that the absorption of an intrinsically labeled $^{10}$B dose from broccoli was complete because 100% of the $^{10}$B dose was recovered in the urine [Vanderpool et al. 1994]. In the human metabolic study described above (Hunt et al. 1994), the amount of boron excreted in the urine of the women fed the low boron...
Western diet (0.36 mg/d) also equalled total daily boron intake. The women may have exhibited obligatory urinary boron losses, an amount of boron equal to 12% of boron intake was also recovered from the feces. If plant and animal boron absorption mechanisms are analogous, the organic forms of boron per se are probably unavailable to humans; the organic forms of boron in soil must be mineralized to be available to plants (Gupta et al. 1985). However, the strong association between polyhydroxyl ligands and boron is easily and rapidly reversed by change in pH, heat or the excess addition of another low molecular polyhydroxyl ligand (Zittle 1951). Thus, within the intestinal tract, most ingested boron is probably converted to B(OH)₃, the normal end-product of hydrolysis of most boron compounds (Greenwood and Earnshaw 1984) and subsequently absorbed.

High boron intakes from typical natural foodstuffs may stimulate an uncharacterized mechanism that limits boron absorption. For example, two ruminant species, cows (Green and Weeth 1977) and sheep (Brown et al. 1989) were found to excrete only 30 and 41%, respectively, of total dietary boron in the urine when fed natural foodstuffs. The boron intakes on a body weight basis were considerably higher in these animals (cow, 0.715 [0.066 mmol]; sheep, 0.667 mg [0.062 mmol] B/kg body wt) than in humans fed 0.36 or 3.23 mg B/day [0.005 mg [0.0005 mmol] or 0.048 mg [0.004 mmol] B/kg body weight respectively).

**Boron transport**

At physiological concentrations, inorganic boron is essentially present in biological fluids only as the mononuclear species B(OH)₃ and B(OH)₄⁻. The uncharged B(OH)₃, probably the dominant boron species in the gut, blood and urine (Spivack and Edmond 1987), forms unique, easily reversible complexes with several biologically important polyhydroxy compounds. These ligands (i.e., riboflavin) typically contain adjacent hydroxyl groups in the cis position (Zittle 1951). The relevant cisoid diol conformations are also present in several biologically important sugars and their derivatives [sugar alcohols, -onic and -uronic acids], such as mannose, ribose, galactose and fructose (Zittle 1951). Therefore, because boron is capable of forming complexes with a large number of ligands, it is doubtful that there is a specific boron transport mechanism. Furthermore, because all available data suggest that ingested boron is well-absorbed, and because the average total daily boron intake (1000–2000 µg [92–184 µmol]) greatly exceeds total blood boron (~213 µg [~19.7 µmol]), blood boron concentrations are probably transiently defined by a single meal and highly influenced by a snack (Vanderpool and Johnson 1992).

**Adequacy of molecular function in relation to boron intake**

To date, five naturally occurring, well-defined, biological boron oxy compounds have been identified; they are all ionophoric macrodiolide antibiotics (Schummer et al. 1994) produced by certain bacteria. There is universal agreement that vascular plants, diatoms and some species of marine algal flagellates have acquired an absolute requirement for boron (Loomis and Durst 1992, Lovatt 1985). Although a specific biochemical role for the element in the metabolism of higher plants remains to be elucidated, the unambiguous characteristics of both boron deficiency and boron toxicity are sufficient to define precisely the boron requirements of many plant species (Lovatt and Dugger 1984).

As described below, findings from numerous studies indicate that animals or humans fed low boron diets (~0.3 mg [0.028 mmol] B/kg), and then fed diets supplemented with inorganic boron, in amounts (~ 2 µg [~0.185 µmol/g] equivalent to that found in diets comprising mainly fruits and vegetables, show changes in several aspects of animal and human physiology. The response to dietary boron was typically more pronounced during concurrent nutritional insult (i.e., vitamin D deficiency). Thus, the endpoints described below, when taken together, can be used to establish a provisional RDA for boron. For the sake of continuity, approaches relevant to human boron depletion-repletion studies, as well as molecular function, are examined together.

**Vitamin D metabolism**

Vitamin D and boron metabolism apparently are closely linked. Boron supplementation of a low boron diet decreased the incidence of mortality in vitamin D-deficient chicks (0 vs. 26%) (Hunt 1989). Furthermore, dietary boron stimulated growth in vitamin D–deficient, boron-deprived chicks but did not markedly affect growth in chicks receiving adequate vitamin D nutrition [Bai and Hunt 1995, Hunt and Herbel 1994, Hunt and Nielsen 1981]. In vitamin D–deficient chicks fed low dietary boron, boron supplementation markedly improved plasma 1,25-dihydroxycholecalciferol concentrations (145 ± 60 vs. 66 ± 30 nmol/L), whereas in the vitamin D–adequate chicks, the boron supplementation decreased these concentrations (126 ± 32 vs. 201 ± 74 nmol/L) (Bakken 1995). In community-based studies with mixed groups of volunteers (men and women on or not on estrogen therapy), boron supplementation (49 d), after consumption of a low boron diet (63 d), increased slightly serum 25-hydroxycholecalciferol [Nielsen et al. 1990, Nielsen et al. 1992] and did not affect serum 1,25 dihydroxycholecalciferol concentrations (Nielsen et al. 1990).
Mineral metabolism

Dietary boron ameliorates the deleterious effects of vitamin D deficiency on several aspects of mineral metabolism through uncharacterized mechanisms. For example, vitamin D deficiency induced elevated concentrations of plasma total alkaline phosphatase activity in the chick (Hunt et al. 1983, Lacey and Huffer 1982). Vitamin D-deficient chicks fed 3.33 mg boron/kg diet, compared with those fed 0.16 mg boron/kg diet, exhibited a 60% reduction in plasma alkaline phosphatase activity (Hunt and Herbei 1994). In the same animals, the boron supplement improved plasma ionized calcium concentrations.

Dietary boron also influences tissue mineral content. For example, in the vitamin D-deficient rat fed a low boron diet, supplemental dietary boron improved the apparent absorption and retention of calcium and phosphorus and increased femur magnesium concentrations (Hegsted et al. 1991). Dietary boron increased femoral calcium and phosphorus concentrations in vitamin D-adequate, but not -inadequate chicks (Hunt et al. 1994). The findings from these two studies indicate that further research is needed to ascertain whether an interaction between boron and vitamin D affects calcium mobilization and retention. Also, in the vitamin D-, boron-deprived rat, supplemental boron (2.87 mg [0.265 mmol] [B/d]) decreased the percent of calcium intake lost in the urine. On the other hand, boron increased the percent of calcium intake lost in the urine of postmenopausal women fed a low magnesium, marginal copper diet (Nielsen et al. 1990). Dietary boron probably affected cardiac mineral metabolism indirectly through unknown mechanisms because it did not affect cardiac boron concentrations.

Dietary boron influences mineral metabolism in humans; the influence is modulated by magnesium nutrition. For example, in postmenopausal women housed in a metabolic unit and fed low amounts of magnesium [109 mg [4.48 mmol] Mg/d] and boron [0.36 mg [0.033 mmol] B/d], supplemental boron [2.87 mg [0.265 mmol] B/d] decreased the percent of calcium intake lost in the urine. On the other hand, boron increased the percent of calcium intake lost in the urine of postmenopausal volunteers fed slightly more than the recommended amount of magnesium [340 mg [14.0 mmol] Mg/d] (Hunt et al. 1994). Boron supplementation also increased urinary calcium loss in both sedentary and athletic free-living premenopausal women consuming self-selected typical Western diets (Meacham et al. 1995). In addition, compared with all other volunteers, sedentary control subjects supplemented with boron exhibited the highest serum total magnesium concentrations. Finally, serum phosphorus concentrations were lower in the boron-supplemented volunteers than in placebo-supplemented volunteers. In a different study of older volunteers fed a marginal copper diet (men and women on or not on estrogen therapy), boron repletion after boron depletion decreased serum calcium and ionized calcium, but not total calcium concentrations (Nielsen et al. 1990).

Boron and growth cartilage and bone metabolism

Boron supplemented to a low boron diet reduced gross bone abnormalities in the vitamin D-deficient chick (Bai and Hunt 1995, Hunt et al. 1994). At the microscopic level, the boron supplement decreased the height of the abnormally thickened growth plate (Hunt 1989, King et al. 1991) and increased chondrocyte density in the proliferative zone of the growth plate in vitamin D-deficient chicks; these findings suggest that boron has some role in the maturation of the growth plate (Hunt et al. 1994). Furthermore, the boron supplement alleviated distortion of the marrow sprouts, a characteristic of vitamin D deficiency (Hunt 1989).

Boron and energy substrate utilization

Dietary boron can significantly ameliorate or remedy certain vitamin D deficiency-induced perturbations in energy substrate utilization in the chick. For example, dietary boron decreases the abnormally elevated concentrations of plasma glucose in the vitamin D-deficient chick (Hunt 1989). In postmenopausal women fed a low magnesium, marginal copper diet (Nielsen 1989), a daily dietary intake of 3.23 mg [0.299 mmol] boron for 49 d, compared with a daily intake of 0.23 mg [0.021 mmol] for 63 d, decreased fasting serum glucose concentrations [in the normal range] approximately 6%.

Boron supplemented to a low boron diet increased the abnormally depressed concentrations of plasma triglycerides in the vitamin D-deficient chick (Hunt and Herbei 1994). In one of the community-based studies mentioned above [Nielsen et al. 1992], boron repletion after a period of boron depletion, also increased serum triglyceride concentrations [in the normal range] approximately 12%. Finally, supplemental boron markedly decreased plasma insulin concentrations in the vitamin D-deprived rat fed a low boron diet (Hunt and Herbei 1991–1992a), and also decreased peak pancreatic insulin secretion by nearly 75% from isolated, perfused pancreata from chicks fed a low boron diet (Bakken 1995).

Human boron depletion/repletion studies

Findings from studies of subjects maintained on diets containing low amounts of boron, followed by correction of the deficit with measured amounts of boron, were summarized above as an integral part of the discussion on assessment of molecular function. With few exceptions, findings from these studies mirror those from other boron deprivation studies with animals. As was the case for evidence of physiological function, it is suggested that the endpoints described for human depletion/repletion boron studies, when
taken together, can be used to establish a provisional boron RDA.

**Suggested approaches for assigning a provisional RDA for boron**

In summary, there is sufficient information to estimate average boron consumption by adult Americans (between 1 and 2 mg/d), adequate understanding of boron status in relation to intake, and a clear indication that boron, in amounts typically consumed, affects mineral metabolism and energy substrate utilization. Taken as a whole, the experimental boron nutrition research data indicate an essential role for the element and a need for a provisional RDA, or similar status category, for this element. The approach to use in the determination of a provisional RDA should include consideration of daily boron intake, boron status in relation to boron intake and the response of human volunteers to boron supplementation after a period of boron depletion.

**CHROMIUM**

In 1957, Schwarz and Mertz reported that a compound, termed glucose tolerance factor, restored impaired glucose tolerance in rats fed a torula yeast diet. Chromium was identified as the critical substance that potentiated insulin action (Schwarz and Mertz 1959). Since that time, chromium supplementation has been reported to correct chromium depletion in three patients receiving total parenteral nutrition [TPN] [Brown et al. 1986, Freund et al. 1979, Jeejeebhoy et al. 1977]. Chromium supplementation generally, but not always, has relieved symptoms of impaired glucose tolerance in humans [Mertz 1993].

Chromium is present in biological tissues in very low concentrations; this makes contamination a major problem in a clinical setting (Veillon 1989). Over the years, the reported concentration of chromium in serum and urine has decreased by at least three orders of magnitude. The lower values reflect improvements in analytical instruments and greater attention to the sources of chromium contamination in sample collection and analysis. Chromium values for biological samples reported before 1980 are generally inaccurate.

**Past recommendations for chromium in the Recommended Dietary Allowances**

The first ESADDI for chromium appeared in the 9th edition of the Recommended Dietary Allowances [NRC 1980]. The ESADDI remained at 50–200 μg [0.96–3.85 μmol]/d for adults in the 10th edition [NRC 1989]. The ESADDI established for infants was 10–40 μg [0.19–0.77 μmol] Cr/d for the first 6 mo and 20–40 μg [0.38–0.77 μmol] Cr/d for 6–12 mo. The ESADDI established for young children was 20–80 μg [0.38–1.54 μmol] Cr/d and for adolescents is 30–120 μg [0.58–2.31 μmol] Cr/d.

**Dietary chromium sources and usual intakes**

Meat, poultry, fish and especially dairy products tend to be low in chromium. Fruits, vegetables and grain products have variable chromium concentrations [Anderson et al. 1992]. Pulses, seeds and dark chocolate may contain more chromium than most other foods [Jorhem and Sundstrom 1993]. Certain spices such as black pepper contain high concentrations of chromium but contribute little to the usual diet on a per serving basis [Anderson et al. 1992]. Loss of chromium in the process of refining sugar has been noted [Wolf et al. 1974]. However, processing also may add chromium to the food supply. Chromium is leached from stainless steel containers particularly when contents are acidic [Offenbacher and Pi-Sunyer 1983]; some brands of beer contain significant amounts of chromium, presumably some comes from the brewing vessels [Anderson and Bryden 1983]. Processed meats also apparently gain chromium during manufacture [Anderson et al. 1992].

In addition to the variable chromium concentrations found in foods, there are differences in bioavailability and biological activity of chromium in various complexes [Mertz et al. 1974]. The best known chromium complex is the glucose tolerance factor; this complex has not been characterized but has been suggested to contain nicotinic acid, glycine, glutamate and cysteine [Mertz et al. 1974]. A low-molecular-weight chromium binding material also has been identified in bovine colostrum but availability of such a complex in mature milk is not known [Yamamoto et al. 1988].

Chromium intakes for many people are below the lower range of the ESADDI [Anderson and Kozlovsky 1985, Bunker et al. 1984, Gibson and Scythes 1984, Offenbacher et al. 1986]. Otherwise adequate diets can be formulated with less than 16 μg [0.31 μmol] Cr/4.0 MJ [Anderson and Kozlovsky 1985]. Using self-selected diets composited for 7 d and analyzed for chromium, the mean chromium intake of 10 adult males was 33 μg [0.63 μmol]/d [range 22–48 μg [0.42–0.92 μmol]] and intake for 22 females was 25 μg [0.48 μmol]/d [range of 13–36 μg [0.25–0.69 μmol)] [Anderson and Kozlovsky 1985]. Overall, the above-mentioned studies have found 22–100% of the subjects to have chromium intakes less than 50 μg [0.96 μmol]/d.

**Factors affecting chromium utilization**

Intestinal absorption of trivalent chromium is low with estimates in fasted rats ranging from <0.5 to 2–3% [Davis et al. 1995, Mertz 1969]. In a metabolic balance study, two men consuming an average of 36.8
generally increased tissue chromium in mice (Seaborn and Stoecker 1989). Absorption of 51Cr was elevated in zinc-deficient rats and was reduced by zinc administration compared with when they consumed only 15% of total calories from simple sugars (Kozlovsky et al. 1987). Subjects who consumed high sugar (35% of total calories) generally had increased urinary chromium excretion compared with when they consumed only 15% of total calories from simple sugars (Kozlovsky et al. 1986). Compared with simple sugars, starch feeding generally increased tissue chromium in mice (Seaborn and Stoecker 1989). Absorption of 51Cr was elevated in zinc-deficient rats and was reduced by zinc administration (Hahn and Evans 1975). Oxalate increased and phytate decreased 51Cr in blood, whole body, and urine of rats 24 h after dosing (Chen et al. 1973).

Common medications can enhance or impair chromium absorption. Rats dosed orally with 40 mg [0.222 mmol] of aspirin exhibited markedly enhanced absorption of 51Cr from 51CrCl3 (Davis et al. 1995). Intraperitoneal injection of 5 mg indomethacin [0.014 mmol]/kg body wt significantly increased 51Cr in blood, tissues and urine of rats; this indicates that blocking the synthesis of prostaglandins enhances chromium absorption (Kamath et al. 1995). Acute administration of several antacids concomitantly with 51CrCl3 significantly reduced 51Cr in blood and tissues compared with controls (Davis et al. 1995, Seaborn and Stoecker 1990).

Much of the chromium in blood is transported by transferrin (Hopkins and Schwarz 1964). Iron uptake on apo-transferrin was reduced in vitro by either aluminum or chromium (Moshthaghe et al. 1992). Likewise rats injected intraperitoneally with 1 mg [0.019 mmol]/kg chromium as chromium chloride daily for 45 d had significant reductions in serum iron, total iron-binding capacity and ferritin and in hemoglobin and hematocrit (Ani and Moshtaghie 1992).

Two patients on low chromium TPN had weight loss that was restored with chromium supplementation (Freund et al. 1979, Jeejeebhoy et al. 1977). Peripheral neuropathy was seen in one of the patients and was reversed with chromium supplementation (Jeejeebhoy et al. 1977).


**Chromium toxicity**

Chromium is a transition element that can occur in a number of valence states including 0, +2, +3 and +6; chromium (III) is the most stable form in biological systems (Cohen et al. 1993, Losi et al. 1994, Mertz 1969). Chromium (VI) is a strong oxidizing agent that comes primarily from industrial sources (Von Burg and Liu 1993). Chromium (VI) consumed in small amounts is reduced to chromium (III) in the acidic environment of the stomach (Mertz 1969; O'Flaherty 1994; Sayato et al. 1980). Because trivalent chromium chloride is poorly absorbed, high oral intakes would be necessary to attain toxic levels (Mertz 1969).

Tannery workers exposed to chromium (III) have elevated body loads of chromium, but the chromium is excreted rapidly in the urine (Randall and Gibson 1987). Toxic effects of industrial exposure have been attributed primarily to airborne chromium (VI) compounds including those obtained from welding stainless steel (IPCS 1988, Katz and Salem 1993, Von Burg and Liu 1993). Toxicity symptoms included allergic dermatitis and increased incidence of lung cancer (Losi et al. 1994, Nethercott et al. 1994, O'Flaherty 1994, Von Burg and Liu 1993).

**Basis for dietary chromium recommendations**

Because no enzyme has been identified as an indicator of chromium status and because of the very low concentrations of chromium in accessible tissues, it has not been possible to monitor status of a large group of subjects with variable chromium intakes. Long-term consequences of dietary intakes <50 μg [0.96 μmol]/d need to be determined because many people in the United States consume <50 μg chromium/d (Anderson et al. 1993b, Anderson and Kozlovsky 1985, Offenbacher 1992). Despite an increase in impaired glucose tolerance with age, age per se apparently is not a risk factor for chromium deficiency (Offenbacher 1992).

When the original ESADDI for chromium was established in 1980, most data on chromium concentrations in food, serum and urine had been obtained without using the types of background correction currently available on instruments; many early data are too high because of analytical problems and contamination (Anderson 1987, Guthrie et al. 1978, Veillon et al. 1982). Currently available data suggest a recommendation...
lower than the 50–200 µg [0.96–3.85 µmol]/d for adults.

There are very few reports that provide information on which to base future recommendations. In one study, subjects were fed low chromium diets (<20 µg [0.38 µmol]/d) for 14 wk. After 4 wk, 200 µg [3.85 µmol] chromium (as CrCl₃) or placebo was randomly assigned for 5 wk in a crossover trial. Chromium supplementation had no affect in subjects with normal glucose tolerance and on which to base future recommendations. In one study, subjects were fed low chromium diets (<20 µg [0.38 µmol]/d) for 14 wk. After 4 wk, 200 µg [3.85 µmol] chromium (as CrCl₃) or placebo was randomly assigned for 5 wk in a crossover trial. Chromium supplementation had no affect in subjects with normal glucose tolerance and diabetes/d was sufficient to prevent impaired glucose tolerance in the control group, but how long normal glucose tolerance could be maintained on such a low chromium intake is unknown.

Based on current data, an infant consuming 750 mL of human milk would receive less than 1 µg [0.019 µmol] chromium/d (Anderson et al. 1993a, Casey and Hambridge 1984, Kumpulainen 1992). There is no indication of enhanced absorption of chromium from human milk compared with formula; this suggests that the ESADDI of 10–40 µg [0.19–0.77 µmol] chromium/d for infants is too high. There are no specific data on which to base a recommendation for children or adolescents.

Suggested approaches for establishing dietary guidance for chromium. Identification of a sensitive indicator of chromium status that could be used in a clinical setting would promote the collection of additional data needed to determine a RDA for chromium. Effects of trivalent chromium on regulation of insulin receptors and on transport of iron by transferrin need evaluation. Additional studies seeking and utilizing sensitive endpoints for biological function of chromium are critically needed. Until then, the provisional RDA, or similar status category, for chromium should be based on usual dietary intakes determined by analyses that avoid all sources of chromium contamination. In addition, insulin and glucose tolerance responses to small supplements (similar to usual dietary intakes) of chromium by individuals fed low chromium diets could be used in establishing the provisional RDA until a more specific indicator of chromium status is determined.

**FLUORIDE**

Fluoride is the ionized form of the element fluorine and these terms are used interchangeably in the following discussion. Fluorine is distributed in water, soil, plants and animals, but concentrations are highly variable in different areas of the country.

A negative correlation between tooth decay in children and the fluoride concentration of their drinking water was demonstrated many years ago [Dean et al. 1942]; this negative correlation has been confirmed by a number of studies [Burt 1982]. However, concerns have surfaced recently about excessive fluoride intakes, particularly from various dentifrices and the potential for fluorosis [Pendrys and Katz 1989]. An additional area of current research is evaluation of the efficacy of pharmacologic doses of fluoride in the treatment of osteoporosis [Hedlund and Gallagher 1989, Pak et al. 1986, Pak et al. 1994, Resch et al. 1993, Riggs et al. 1994].

**Past recommendations for fluoride in the Recommended Dietary Allowances**

In the 10th edition of the Recommended Dietary Allowances [NRC 1989], the ESADDI established for fluoride for adults was 1.5–4.0 mg [0.08–0.21 mmol]/d. The ESADDI established for infants was between 0.1 [0.005] and 1.0 mg [0.053 mmol] F/d. For children and adolescents the ESADDI varied between 0.5–2.5 [0.026–0.132] and 1.5–2.5 mg [0.079–0.132 mmol] F/d, respectively [NRC 1989]. Fluoride was given an ESADDI on the basis of its beneficial effects on dental caries rather than clear-cut evidence of essentiality [NRC 1989].

**Dietary fluoride sources and usual intakes**

Both tea and small marine fish consumed with their bones are rich sources of fluoride [Kumpulainen and Koivistoinen, 1977]. Most of the variation in dietary fluoride intake stems from beverages. The fluoride concentration of drinking water varies widely within the United States; public health organizations recommend that fluoride concentrations of the drinking water should be between 0.7 [0.037] and 1.2 mg [0.063 mmol]/L [NRC 1989].

Cow's milk and human milk are low in fluoride. Manufacturers of concentrated infant formulas have agreed to prepare the formulas without added fluoride and assume that fluoridated water will be used for reconstitution of the formulas. Infants in the United States may consume 100 µg [5.26 µmol] F·kg⁻¹·d⁻¹ from concentrated liquid formulas diluted with fluoridated water and 150 µg [7.89 µmol] F·kg⁻¹·d⁻¹ from powdered formulas diluted with fluoridated water [Ekstrand et al. 1994].

**Factors affecting fluoride utilization**

Most fluoride is incorporated in the bones and teeth; fluoride incorporation is thought to be proportional to intake. In infants, retention of a fluoride dose ranged from 75 to 87% [Ekstrand et al. 1994]. This retention is higher than that seen in adults and may indicate that the infant has a greater capacity to deposit fluoride in...
bone than the adult [Ekstrand et al. 1994]. The primary route of excretion of fluoride is the kidney.

Toxicity

Chronic toxicity of fluorine is called fluorosis; this condition has increased in recent years [Pendrys and Katz 1989; Pendrys et al. 1994]. Enamel fluorosis was strongly associated with fluoride supplementation during the first 6 y of life and with fluoride dentifrice use [Pendrys and Katz 1989]. Fluorosis ranges from barely perceptible white striations to brownish stains [Committee on Nutrition 1995]. The brownish mottling of teeth is a very obvious result of excessive fluoride in the water supply [Segreto et al. 1984].

Fatal fluoride intoxication was observed in hemodialysis patients because of malfunction of a deionization system used to purify dialysis solutions. With normal renal function a serum fluoride of <2 μmol/L would be expected; the hemodialysis patients who suffered acute illness or death had serum fluoride concentrations of 59–716 μmol/L. Symptoms of toxicity included severe pruritus, headache, nausea and fatal ventricular fibrillation [Arnow et al. 1994].

Basis for fluoride recommendations

When daily intakes of fluoride in infants were less than 2.6 μg [0.137 μmol/kg body wt, urinary fluoride exceeded intake; this indicates that fluoride was being released from the bone [Ekstrand et al. 1994]. When fluoride was supplemented, intakes of fluoride from a single feeding plus the supplement averaged 36.6 μg [1.93 μmol/kg] and infants were always in positive balance. Mean plasma peak fluoride concentration was 3.3 μmol/L at this level of supplementation [Ekstrand et al. 1994].

In 1995 the American Academy of Pediatrics published modified recommendations for fluoride supplementation for children. Fluoride supplementation is no longer recommended from birth and suggested doses have been decreased during the first 6 y of life. If water fluoride concentrations are >0.6 μg [0.032 μmol/mL], fluoride supplements are not recommended [Committee on Nutrition 1995]. Additional guidelines from the Canadian Dental Association recommend that children should use only a ‘pea-sized’ amount of fluoride-containing dentifrice and that this dentifrice should be used no more than twice daily [Clark 1993].

Another pharmacologic application of fluoride is in the treatment of postmenopausal osteoporosis. Compared with a placebo, a dose of 75 mg [1.79 mmol] sodium fluoride/d increased mineral density in the lumbar spine and other predominantly cancellous bone sites; however cortical bone was decreased and nonvertebral fractures were higher in the treatment group [Riggs et al. 1990]. Subsequently, studies using lower doses or slow-release sodium fluoride (25 mg [0.60 mmol] twice daily) combined with calcium supplementation have shown lower vertebral and peripheral fracture rates [Pak et al. 1994; Prestwood et al. 1995; Resch et al. 1993]. Further research is needed to clarify the “therapeutic window” for blood fluoride levels that is not associated with skeletal fragility or the painful lower extremity syndrome [Kleerekoper and Mendlovic 1993].

Suggested approaches for establishing dietary guidance for fluoride

Recommendations for fluoridation of the water supply should consider reduction in dental caries vs. incidence of enamel fluorosis. Fluoride balance data throughout the life cycle are needed to establish optimal fluoride intakes.

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