

Is boron nutritionally relevant?

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Evidence from numerous laboratories using a variety of experimental models, including humans, shows that boron is a bioactive beneficial element. Much evidence has come from studies that did not require nutritional or environmental stressors or fastidious methods in diet preparation or environmental control. The evidence includes deprivation studies showing that boron is necessary for some higher animals to complete the life cycle, and that realistic low boron intakes result in impaired bone health, brain function, and immune response. Thus, low boron intake is a relevant nutritional concern, which diets rich in fruits, vegetables, nuts, and pulses can prevent.

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INTRODUCTION

Numerous questions are quite often raised when the nutritional relevance or importance of boron is considered, including the following. Are not responses to boron deprivation achieved only by feeding diets made boron-low through specially selected or prepared ingredients, or diets possessing some stressor such as a marginal or deficient intake of another nutrient, and by using special environments including plastic caging and filtered air? Therefore, how can an inadequate intake of the “ultra trace” element boron be likely under normal living conditions? In addition, how can boron be considered nutritionally relevant or essential when it does not have a defined biochemical function, and boron intakes have not been associated with any human pathology? These questions are understandable because boron often is placed in a list that includes ultra trace elements for which most of these questions are justifiable. However, an increasing number of findings from numerous research groups throughout the world indicate that these questions about boron may not be justified, and that boron may be just as relevant for promoting health as some other bioactive food substances receiving attention for such a role (i.e., long-chain polyunsaturated omega-3 fatty acids, carotenoids, coenzyme Q₁₀).

EARLY HISTORY OF BORON IN FOODS AND NUTRITION

Since 1857, boron has been known to be present in plants. Reports by Warington¹ in 1923 and Sommer and Lipman² in 1926 resulted in the acceptance of boron as an essential nutrient for plants because it was necessary to complete the life cycle. Interestingly, over 80 years have past and a clearly defined biochemical function has not been identified for boron in the reproductive process of plants. Boron does have a structural role in plant cell walls;³ thus, boron is a constant constituent of foods of plant origin.

In the 1870s, it was discovered that sodium borate and boric acid could be used to preserve foods. For about the next 50 years, borate addition was considered one of the best methods for preserving or extending the palatability of foods such as meat and dairy products. Boron had a vital role as a preservative in preventing food crises during both World War I and II. Boron apparently was considered relatively non-toxic because no deaths were attributed to using boron as a preservative. However, as early as 1902, German and American scientists began to question the orthodox view that large amounts of borates in foods were innocuous. Foremost among the reports that changed perceptions about boron was that presented by Wiley⁴ in 1904. He indicated that consumption of boric acid in doses greater than 500 mg/day (87 mg

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B/day) for 50 days resulted in disturbances in appetite, digestion, and health in human volunteers, and he concluded that 4000 mg/day (699 mg B/day) was the limit beyond which a normal man cannot go without harm. Subsequent to his report, the opinion that boron posed a risk to health gained momentum. By the mid-1920s, many countries of the world began legislating against the addition of borates to food; these restrictions were eased during World War II. After the war, restrictions were gradually re-imposed. By the 1950s, boron as a food preservative was essentially forbidden throughout the world.

About 15 years after boron was accepted as essential for plants, attempts were made to show boron essentiality for animals. Depression of growth and survival of pups of rats fed low-boron diets were used to assess the nutritional essentiality of boron.^{5,6} The survival of nursing pups in both boron-low and -supplemented groups was not good in these early studies. Recent research has found that boron deprivation does not markedly affect growth. Thus, measures used in early studies to determine whether boron is essential were unsuitable. Nonetheless, the lack of success in describing a deficiency sign in response to boron deprivation resulted in generations of students in biochemistry and nutrition being taught that boron was a unique element in that it was essential for plants but not for higher animals and humans.

In the early 1980s, the dogma about boron not having any nutritional benefits in higher animals and humans began to change. This is when a study in my laboratory showed that boron deprivation exacerbated gross bone abnormalities in chicks fed marginal amounts of vitamin D.⁷ Subsequently, Hunt⁸ found that boron deprivation exacerbated the distortion of marrow sprouts (location of calcified scaffold erosion and new bone formation) and number of osteoclasts within marrow sprouts of the proximal tibial epiphyseal plate; in addition, it delayed initiation of cartilage calcification induced by marginal vitamin D. Hunt also found that boron deprivation without a marginal vitamin D intake decreased chondrocyte density in the zone of proliferation of the growth plate of chicks.⁹ The findings with chicks stimulated further studies with a variety of species including humans, rats, frogs, zebrafish, pigs, and mice.

DIETS AND ENVIRONMENTS FOR BORON DEPRIVATION STUDIES

Early studies of boron deprivation used diets prepared with ultra pure minerals and specially prepared dietary ingredients such as acid-washed ground corn, and all-plastic environments with HEPA-filtered air to assure a consistent low intake of boron. Later studies, however, negated the perception that these fastidious methods are necessary to achieve a low boron status that responds to

nutritional amounts of boron. For example, responses to nutritional amounts of supplemental boron have been reported for rats fed the AIN-76 basal rodent diet,¹⁰⁻¹¹ pigs fed a semi-purified diet made from commercially available ingredients,¹² and humans fed a Western diet made of commonly consumed foods.^{13,14} Commonly used animal caging and environments have been used in boron deprivation experiments.^{10-12,15-19} These reports reveal that inducing a low boron status requires only the techniques used to induce deficiencies of other trace elements or vitamins. These techniques include the use of commercial dietary ingredients low in boron, so a diet containing less than 0.5 mg/kg (may be slightly higher for pigs) is used, avoiding water that contains significant amounts of boron and environments that may inadvertently provide a source of boron (e.g., paper, wood shavings).

ESSENTIAL AND BENEFICIAL ACTIONS OF BORON

Boron has been found essential for some organisms in all phylogenetic kingdoms. Among the higher animals that require boron to complete their life cycle are zebrafish and frogs. Boron deprivation or 0.045–0.062 mg compared to 0.31–1.85 mg/kg diet, of adult male and female frogs disrupted reproduction.^{16,17} Boron-deprived males exhibited atrophied testes, decreased sperm counts, and sperm dysmorphology. Female frogs exhibited atrophied ovaries and impaired oocyte maturation. Boron deprivation resulted in a marked increase in necrotic eggs and a high frequency of abnormal gastrulation characterized by bleeding yolk and exogastrulation. More than 80% of the embryos from frogs fed the boron-deficient diet for 120 days died before 96 hours of development; survival of embryos at 96 hours from the boron-adequate frogs exceeded 75%. Differences in embryogenesis occurred in zebrafish fed boron-depleted brine shrimp and maintained for six months in water containing only 0.1 μmol B/L compared to those maintained in water containing about 45 μmol B/L.¹⁸ The early cleavage stage of development was most sensitive to boron deficiency; 46% of fertilized boron-deficient embryos did not complete the blastula stage compared to 2% for boron-adequate embryos. During this time of rapid cell division, the boron-deficient zygotes exhibited blebbing of cell membranes, followed by cytoplasmic and yolk extrusion. Adult F₁ boron-deficient zebrafish exhibited photophobia.¹⁹

Although there are data suggesting that boron deprivation impairs early embryonic development in mice,²⁰ the critical experiment demonstrating that boron is essential for a mammal to complete the life cycle, or defining a biochemical role for boron necessary for life, is lacking. However, the status of boron for higher animals and humans may be considered similar to that of the

long-chain polyunsaturated omega-3 fatty acids, which promote health but do not have a clearly defined biochemical function and whose lack has not been shown to interrupt the life cycle. Nutritional amounts of dietary boron, or >1 mg/kg but not much higher than 15 mg/kg (close to that found in commercial animal chows and feeds), compared to dietary boron at 0.1–0.5 mg/kg, have been found to induce biochemical and functional changes often considered beneficial, particularly for bone growth and maintenance, brain function, and inflammatory response regulation in higher animals. For humans, boron intakes of 1–3 mg/day compared to intakes between 0.25 and 0.50 mg/day reportedly have beneficial effects on bone and brain health.

BORON AND BONE

Considerable evidence exists to support the contention that boron has beneficial effects on bone, especially trabecular and alveolar bone, in ways that are independent of any other nutritional stressor. The most recent findings showing boron alone is beneficial to alveolar and trabecular bone have been submitted or accepted for publication but at present are described only in abstracts;^{21–23} some preliminary results are presented in a publication of symposium proceedings.²⁴ In one study,^{21,24} the fourth lumbar vertebrae from 12 male rats exposed to boron deprivation (0.1 mg/kg diet) from conception to age 21 weeks were examined by microcomputed tomography (μ CT) and compared to vertebrae from rats fed supplemental boron (3 mg/kg diet). Boron deprivation decreased bone volume fraction and trabecular thickness, and increased trabecular separation and structural model index (a lower value or more plate-like structure is preferable). The μ CT findings indicate that boron is beneficial, if not essential, for trabecular microarchitecture that promotes bone strength. Boron deprivation also was found to impair alveolar bone (primary support structure for teeth) repair, which is initiated immediately after tooth extraction. Compared to rats fed 3 mg B/kg diet, rats fed diets containing 0.07 mg B/kg had decreased alveolar bone (decreased bone volume fraction in the alveolus) 14 days after tooth extraction.^{22,25} Histological examination revealed that boron deprivation decreased osteoblast surface and increased quiescent bone-forming surface in the alveolus. Boron deprivation without tooth extraction also impaired alveolar bone formation. Mice fed a boron-deficient diet (0.07 mg/kg) for 9 weeks, compared to mice supplemented with a 3 mg B/kg diet, exhibited decreased osteoblast surface and increased quiescent bone-forming surface in both the lingual and buccal side of periodontal alveolar bone.²³ These findings have led to the development of a bioactive glass containing boron;²⁶ bioactive glass is used as a scaffold for bone tissue engi-

neering and for in situ bone tissue regeneration. When the bioglass 45S5 was modified to contain boron, bone formation was enhanced.

Reported findings indicating that boron is beneficial to bone strength include boron deprivation decreasing the bone strength variables determined by a three-point bending test of femurs of female rats, particularly when they were fed canola oil,²⁷ and in femurs of pigs.^{12,28}

Interestingly, boron deprivation does not markedly affect the calcium and phosphorus concentrations in bone. Instead, boron deprivation affects the concentrations of mineral elements (e.g., magnesium, potassium, copper, zinc)^{24,27} associated with the formation, differentiation and activity of osteoblasts and osteoclasts. The mineral changes in bone, in addition to boron deprivation decreasing alveolar bone osteoblast surface in rats and mice and chondrocyte density in the growth plate zone of proliferation of chicks, and inducing limb teratogenesis in frogs,²⁹ suggests that boron is beneficial to the bone growth and maintenance through affecting osteoblast and/or osteoclast presence or activity and not through affecting bone calcium concentration.

Although boron deprivation alone impairs functional, physical, and elemental concentration characteristics of bone, the effects of boron often are enhanced by modifying environmental or dietary factors also involved in bone formation and maintenance. The use of modifiers of bone formation and turnover to enhance the effects of dietary boron or to gain insight into the possible locus of boron action probably has detracted from the realization that boron does not need modifiers to be shown beneficial to bone formation and maintenance. Nonetheless, findings with the use of modifiers may be providing clues about the mechanism through which boron has beneficial, perhaps essential, action in higher animals and humans. Among these findings are those indicating that boron promotes the efficacy of some bone-associated hormones.

Several studies have shown that when animal models are fed marginal amounts of vitamin D, classical signs of vitamin D deficiency related to bone and calcium metabolism are exhibited with dietary boron deprivation but not with nutritional amounts of dietary boron. These signs include rachitic long bones⁷ with distortion of marrow sprouts and delayed initiation of cartilage calcification,⁸ decreased calcium and phosphorus apparent absorption and balance,³⁰ increased plasma glucose and triglycerides,⁹ and decreased growth and femur calcium concentration.³¹

Boron has been shown to increase the efficacy of estrogen supplementation in both rats and humans. In ovariectomized rats fed an AIN-76 diet containing 0.4 mg B/kg, a 5 mg B/kg diet supplement significantly increased the beneficial effect of 17 β -estradiol supplementation on

trabecular bone volume fraction, bone growth plate density, and trabecular separation.¹¹ The combination of boron and 17 β -estradiol, versus either of these alone, also markedly improved the apparent absorption of calcium, phosphorus and magnesium, and the retention of calcium and magnesium.¹⁰ Boron supplementation alone did not significantly improve any of these variables in the ovariectomized rats. This finding is not unique, because others have found that boron supplementation of a boron-low diet does not markedly affect numerous bone status indicators altered by ovariectomy.^{32,33}

This lack of an effect may be indicating that estrogen was too limited for boron to have a major impact on improving bone turnover by increasing the efficacy of estrogen. In postmenopausal women, the increases in serum 17 β -estradiol and plasma copper induced by estrogen therapy were significantly higher when they consumed 3.25 mg B/day instead of 0.25 mg B/day.³⁴ The higher boron intake also enhanced the effect of estrogen therapy on serum triglyceride and immunoreactive ceruloplasmin concentrations. Additionally, the combination of estrogen therapy with the higher boron intake was most effective in increasing serum 25-hydroxycholecalciferol concentration.

BORON AND BRAIN

Findings showing that nutritional intakes of boron have beneficial effects on central nervous function are more limited than those with bone. However, they are among the most supportive in demonstrating that boron is a beneficial bioactive element for humans. Boron deprivation of older men and women altered electroencephalograms (EEG) such that there was a shift toward more activity in the low frequencies and less activity in the high, dominant frequencies of the EEG spectrum.^{35,36} A similar effect was also found in rats.³⁷ The EEG changes induced by boron deprivation is similar to that found in non-specific malnutrition and heavy metal toxicity. Increased low-frequency activity is typical of states of reduced behavioral activation (i.e., drowsiness) and mental alertness, and has been associated with reduced performance in vigilance and psychomotor tasks. Decreased high-frequency activity has been associated with impaired memory performance. Some of these possible behavioral consequences of a changed EEG spectrum induced by boron deprivation were found by Penland.³⁶ Boron deprivation impaired measures of cognitive processes of Search-Count (attention) and Symbol-Digit (encoding skills and memory), and the psychomotor skill measure of tapping keys on a computer (indicates manual dexterity and fatigue).

Recently it was found that boron deprivation alters rat behavior and brain mineral composition differently

when dietary fat (75 g/kg) was supplied as fish oil (65 g/kg plus 10 g/kg linoleic acid) instead of safflower oil.¹⁵ Boron-deficient (0.1 mg/kg diet) rats were less active than boron-adequate (3.1 mg/kg diet) rats when fed safflower oil based on reduced number, distance, and time of horizontal movements, front entries, margin distance, and vertical breaks and jumps in a spontaneous activity evaluation. Feeding fish oil instead of safflower oil attenuated the activity response to boron deprivation.

BORON AND THE INFLAMMATORY OR IMMUNE RESPONSE

Several laboratories have found that boron status affects the response to injury or infection. Among the findings is that of boron status affecting the response to injected antigens. When injected with an antigen (*M. butyricum* in mineral oil) to induce arthritis, boron-supplemented (2.0 mg/kg diet) rats had less swelling of the paws and lower circulating concentrations of natural killer cells and CD8a⁺/CD4⁻ cells than did boron-deficient (0.1 mg/kg diet) rats.³⁸ Another study found that boron supplementation (20 mg/kg diet) of a boron-low (0.2 mg/kg) diet significantly delayed the onset of adjuvant-induced (*M. tuberculosis*) arthritis in rats.³⁸ Pigs fed a boron-low (1–2 mg/kg) diet for 95 days exhibited a significantly higher skinfold thickness response to an intradermal injection of phytohemagglutinin than pigs supplemented with boron (5 mg/kg diet).³⁹ Physiological amounts of boron (3 mg/kg) supplemented to a boron-low diet (0.2 mg/kg) more than doubled the serum total antibody concentrations to injected antigen (human typhoid vaccine) in rats.⁴⁰

The suggestion that boron may have a regulatory role in the inflammatory or immune response is supported by a recent study of mice infected with the nematode *H. bakeri*.⁴¹ Boron deprivation downregulated 30 of 31 cytokines or chemokines associated with the inflammatory response six days post-primary-infection. An opposite pattern was found, especially 21 days post-challenge; mice consuming low and marginal boron-deficient diets had >100% increases in 23 of 31 cytokines determined. This finding is consistent with lower serum tumor necrosis factor- α and interferon- γ after lipopolysaccharide injection in pigs fed a marginal boron-deficient diet than in pigs supplemented with a 5 mg boron/kg diet.⁴²

Boron status also affects the populations of blood cells involved in the immune or inflammatory response. Perimenopausal women excreting an average of 1.1 and 3.0 mg boron/day during placebo and boron supplementation periods, respectively, had increased white blood cell numbers, an increased percentage of polymorphonuclear neutrophils, and a decreased percentage of lymphocytes during the boron supplementation period.⁴³

Boron status also affects changes in immune cell populations induced by other dietary factors, which include dietary fatty acids. Supplementation of young healthy men with 6 g/day of the n-3 polyunsaturated fatty acid docosahexaenoic acid for 12 weeks decreased the number of white blood cells, mainly because of a decreased granulocyte number; the decreased granulocyte number resulted in an increased percentage of lymphocytes in the white blood cells.⁴⁴ In contrast, 1.5 g of the n-6 polyunsaturated fatty acid increased granulocyte numbers.⁴⁵ Compared with safflower oil (mostly n-6 polyunsaturated fatty acids), fish oil (high in n-3 polyunsaturated fatty acids) increased white blood cell numbers, with most of the increase in the lymphocyte fraction, in boron-adequate (3 mg/kg diet) rats but not in boron-deprived (0.1 mg/kg diet) rats.⁴⁶ Fish oil instead of safflower oil increased monocyte and basophil numbers in boron-deprived but not in boron-adequate rats. Similarly, canola oil (high in n-3 fatty acids) increased the percentages of white blood cells that were basophils and monocytes in boron-deprived rats, but not in boron-adequate rats.⁴⁷

An effect on the inflammatory response might be the reason that boron was found beneficial in a study of 20 patients with radiographically confirmed osteoarthritis consuming daily either a 6 mg boron supplement or a placebo for 8 weeks in a double-blind trial.⁴⁸ The boron-supplemented arthritic individuals self-reported substantial improvement in subjective measures of joint swelling, restricted movement, and fewer analgesics for pain relief.

Affecting the immune response might be the reason that boron intake has been associated with some cancers. Based on a study of 95 cases and 8720 controls, low dietary boron intake was associated with increased prostate cancer risk.⁴⁹ The protective effect of boron became stronger with increasing amounts of boron consumed as a constituent of foods. Boric acid in concentrations similar to that in blood was found to inhibit the proliferation of human prostate cancer cell lines DU-145 and LNCaP in vitro.⁵⁰ Cervical smears of 472 women with a high mean boron intake (8.41 mg/day) and 587 with a marginal mean boron intake (1.26 mg/day) found 15 cases of cytopathological indications of cervical cancer in boron-low women and none in the boron-high women.⁵¹ Low dietary boron has also been associated with some types of breast cancer.⁵²

BORON AND HORMONE FUNCTION

In addition to estrogen and vitamin D described above, there is evidence that boron status affects the presence or function of other hormones, including thyroid hormone, insulin, and progesterone. Boron deprivation decreased the rate of tail absorption in larvae during their develop-

ment into frogs. Addition of 100 fg thyroxine/L of medium, a known enhancer of tail resorption, reversed the delayed tail absorption.¹⁷ In pigs, supplementing a low-boron diet (1–2 mg/kg) with 5 mg boron/kg during the nursery and growth stage, decreased serum triiodothyronine and thyroxine.³⁹ Boron supplementation (2.5 mg/day) for 90 days decreased serum triiodothyronine in perimenopausal women after consuming a placebo for 90 days.⁴³

Boron supplementation (2 mg/kg diet) of rats fed a boron-deficient diet (0.2 mg/kg) reduced plasma insulin but did not change plasma glucose concentrations.⁵³ Peak insulin release from isolated, perfused pancreata of boron-deprived chicks was almost 75% higher than that from pancreata of boron-supplemented chicks; the difference was especially noticeable when the perfusate was supplemented with glucose.⁵³ These findings suggest that boron may reduce the amount of insulin needed to maintain plasma glucose.

Incomplete frog oocyte maturation caused by boron deficiency could not be induced to mature by the administration of exogenous progesterone.⁵⁴ Progesterone successfully induced germinal vesicle breakdown in oocytes from females fed a boron-supplemented diet.

BORON MECHANISM OF ACTION

Boron has no clearly defined biochemical function in higher animals and humans. The problem of pinpointing the primary mechanism of action of boron in higher animals and humans is similar to that for plants. Mainly, the problem is that a wide range of responses associated with a low intake of boron probably represents secondary effects of the primary action of the element. Recent emphasis on finding a biochemical role in plants has focused on a role at the cell membrane level.⁵⁵ The numerous responses of boron-deprived animals and humans to physiological or nutritional amounts of boron also suggest that boron has a role in maintaining structural integrity and/or function of cell membranes. The chemistry of borate (the form of boron occurring in vivo) supports this suggestion. Boron complexes with organic compounds containing hydroxyl groups; the formation is best when hydroxyl groups are adjacent and *cis*. The phosphoinositides, glycoproteins, and glycolipids of membranes contain *cis*-hydroxyl groups. Thus, diester borate polyol complexes may form in membranes that could act as calcium chelators and/or redox metabolism modifiers affecting membrane integrity and function. Thus, a low boron status may impair important cell receptor and signal transduction functions.

A role for boron in maintaining membrane structural integrity is supported by frog and zebrafish findings. In the boron-deprived *Xenopus* model, the abnormal

gastrulation characterized by bleeding yolk and exogastulation suggest disturbed cell membrane structural integrity.^{16,17} The most prevalent pathologic changes before death of boron-deprived zebrafish during the zygote and cleavage periods were extensive membrane blebbing and extrusion of cytoplasm.^{18,19} The changes occurred when cells were producing prodigious amounts of membranes, and they were consistent with membrane alterations reported for boron-deprived cyanobacteria.⁵⁶

The finding that boron changes the ability of some hormones to express their actions supports the suggestion of a role affecting membrane receptors or signal transduction. Boron deprivation apparently decreases insulin sensitivity⁵³ and increases the requirement for vitamin D to prevent gross bone abnormalities⁷ and the need for exogenous thyroxine for tail resorption in frogs.¹⁷ Radio-binding studies found that progesterone binding to *Xenopus* oocyte membrane progesterone receptor was markedly reduced by boron deprivation; washout studies found progesterone binding was also more transient.⁵⁴ In addition to these boron-deprivation studies, a low intake of boron was associated with decreased risk of estrogen receptor-negative breast tumors relative to estrogen receptor-positive tumors.⁵²

Several findings suggest that boron affects the transduction of signals or regulatory ions across cell membranes. The mammalian borate transporter NaBC1, which is essential for cellular boron homeostasis, conducts Na⁺ and OH⁻ across cell membranes in the absence of boron.⁵⁷ At low concentrations, borate activates the MAPK pathway to stimulate growth and proliferation of HEK293 cells in culture. The expression of the Fc receptor, which internalizes antigen-antibody complexes, on mouse macrophages in culture was enhanced by a rhamnogalacturonan II (GL-4IIb2);⁵⁸ the concentration of boron in this rhamnogalacturonan II is relatively high (0.09%). Diadenosine phosphates are present in all cells and function as signal nucleotides associated with neuronal response. Diadenosine phosphates have higher affinities for boron than any other currently recognized boron ligand present in animal tissues.⁵⁹ A bacterial quorum-sensing signal molecule (auto-inducer AI-2) was characterized as a furanosyl borate ester synthesized from adenosylmethionine.⁶⁰ Quorum sensing is the cell-to-cell communication in bacteria that is accomplished through the exchange of extracellular signaling molecules (auto-inducers).

Another indication that boron has action at the cell membrane level is that dietary magnesium and fatty acids, which affect membrane function, influence the response to boron deprivation. For example, boron deprivation increased the percentage of dietary calcium lost in urine in magnesium-deficient postmenopausal women, but decreased the percentage in magnesium-adequate

women.¹⁴ Boron deprivation increased serum calcitonin in magnesium-deficient, but not magnesium-adequate, older men and women.⁶¹ As described above, dietary fatty acids influenced the effect of boron deprivation in animal models on bone strength and structure characteristics, behavior, and immune cell populations. In addition, dietary fatty acids influenced the effect of boron deprivation on brain mineral composition¹⁵ and eye mitochondrial morphology.⁶²

IMPLICATIONS THAT BORON INTAKE AFFECTS HEALTH IN THE POPULATION

The suggestion that boron may be a factor in maintaining health is reasonable because there is evidence that many people consume less boron than has been found to promote bone and brain health. In human depletion-repletion experiments, subjects responded to a boron supplement after consuming a diet supplying only 0.2–0.4 mg boron/day for 63 days,^{14,34–36,61} suggesting that this intake of boron is inadequate. Thus, a dietary boron intake higher than 0.4 mg/day may be beneficial to bone and brain health. Extrapolation of data from animal experiments suggests that 1 mg boron/day would provide optimal nutritional benefits for this element. Both animal and human data were used by the World Health Organization to suggest that an acceptable safe range of population mean intakes of boron for adults could well be 1–13 mg/day.⁶³ Based on published values for boron in foods, it has been estimated that the median intake of boron in the United States is 0.86 mg/day.⁶⁴ The 1994–1996 Continuing Survey of Food Intakes by Individuals indicated that boron intakes ranged from a low of about 0.35 mg/day to a high of about 3.25 mg/day for adults.⁶⁵ The median intakes for various age groups of adults ranged from 0.87 to 1.13 mg/day. The reported median intakes of 0.86 and 0.87 mg boron/day suggest a significant number of people would benefit from increased boron intakes. This suggestion is supported by a study of 43 perimenopausal women in eastern North Dakota.⁴³ Based on urinary excretion of boron (a good indicator of boron intake), two women apparently consumed an average of less than 0.5 mg boron/day, and 14 women consumed between 0.5 and 1.0 mg boron/day.

There are only a few reports associating boron intake or status with diseases other than some types of cancer described above. Low concentrations of boron in hair⁶⁶ and low environmental boron⁶⁷ have been associated with Kashin-Beck disease in China. Low boron status has been associated with rheumatoid arthritis.⁶⁸ Based on the suggestion that a significant number of people may have a low boron status, more epidemiological studies determining whether a low boron intake is associated with some disorders of bone and brain seems prudent.

There are two reports describing no or limited responses by postmenopausal women to boron deprivation, which may have resulted in negative impressions about the nutritional importance of boron. Several aspects of the experimental designs of these studies, however, may have contributed to the lack of marked findings. In one experiment, the subjects were only equilibrated on the experimental diet for two days before starting the low dietary boron regimen that lasted only 21 days.⁶⁹ The data (i.e., increasing urinary calcium) presented from only six subjects suggest that they were still adjusting from their self-selected diets to the experimental diet, and thus to changes in other nutrient intakes when they began receiving boron supplementation of 21 days duration. Additionally, 21 days is an extremely short deprivation period for an adult organism when the diet is not severely deficient and a small number of subjects limits statistical power. In successful boron deprivation experiments, 14 subjects were equilibrated to the experimental diet for 14 days, and the first 21 days of boron deprivation were not included in the analysis because only minimal responses occurred during this time; the most marked effects were seen after 42 days of boron deprivation.^{14,34–36,61} Thus, short boron deprivation periods of only 42 days in a Latin-square experimental design most likely contributed to finding only a limited number of responses to boron deprivation in another human study.⁷⁰ In addition, varying dietary magnesium (deficient and adequate) may have obscured or blunted the effects of varying dietary boron. These design concerns suggest that these two human studies are ill-suited for making an assessment of the nutritional relevance of boron.

CONCLUSION

The evidence that boron is a bioactive beneficial trace element is substantial. The evidence has come from numerous laboratories that have used a variety of experimental models, including humans. Based on some provocative findings, studies determining whether boron has a function at the cell membrane level should be pursued. Findings that boron has been shown to complete the life cycle of some higher animals, and that a realistic low boron intake impairs bone health, brain function, and the immune response, indicate that boron is a relevant nutritional concern. Increased intakes of boron through including fruits, vegetables, nuts, and pulses in the diet should be recognized as a reasonable dietary recommendation.

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REFERENCES

1. Warington K. The effect of boric acid and borax on the broad bean and certain other plants. *Ann Bot* 1923;37:629–672.
2. Sommer AL, Lipman CB. Evidence of the indispensable nature of zinc and boron for higher green plants. *Plant Physiol* 1926;1:231–249.
3. O'Neill MA, Warrenfeltz D, Kates K, et al. Rhamnogalacturonan-II, a pectic polysaccharide in the walls of growing plant cells, forms a dimer that is covalently cross-linked by a borate ester. *J Biol Chem* 1996;271:22923–22930.
4. Wiley HW. Influence of food preservatives and artificial colors on digestion and health. I. Boric acid and borax. *US Department of Agriculture Bulletin No. 84, Pt 1*. Washington, DC: Government Printing Office; 1904.
5. Hove E, Elvehjem CA, Hart EB. Boron in animal nutrition. *Am J Physiol* 1939;127:689–701.
6. Teresi JD, Hove E, Elvehjem CA, Hart EB. Further study of boron in the nutrition of the rat. *Am J Physiol* 1944;140:513–518.
7. Hunt CD, Nielsen FH. Interaction between boron and cholecalciferol in the chick. In: McC Howell J, Gawthorne JM, White CL, eds. *Trace Element Metabolism in Man and Animals (TEMA-4)*. Canberra, Australia: Australian Academy of Science; 1981:597–600.
8. Hunt CD. Dietary boron modified the effects of magnesium and molybdenum on mineral metabolism in the cholecalciferol-deficient chick. *Biol Trace Elem Res* 1989;22:201–220.
9. Hunt CD, Herbel JL, Idso JP. Dietary boron modifies the effects of vitamin D₃ nutrition on indices of energy substrate and utilization and mineral metabolism in the chick. *J Bone Min Res* 1994;9:171–182.
10. Sheng MH-C, Taper LJ, Veit H, Thomas EA, Ritchey SJ, Lau K-HW. Dietary boron supplementation enhances the effects of estrogen on bone mineral balance in ovariectomized rats. *Biol Trace Elem Res* 2001;81:29–45.
11. Sheng MH-C, Taper LJ, Veit H, Qian H, Ritchey SJ, Lau K-HW. Dietary boron supplementation enhanced the action of estrogen, but not that of parathyroid hormone, to improve trabecular bone quality in ovariectomized rats. *Biol Trace Elem Res* 2001;82:109–123.
12. Armstrong TA, Spears JW, Crenshaw TD, Nielsen FH. Boron supplementation of a semipurified diet for weanling pigs improves feed efficiency and bone strength characteristics and alter plasma lipid metabolites. *J Nutr* 2000;139:2575–2581.
13. Nielsen FH, Mullen LM, Gallagher SK. Effect of boron depletion and repletion on blood indicators of calcium status in humans fed a magnesium-low diet. *J Trace Elem Exp Med* 1990;3:45–54.
14. Hunt CD, Herbel JL, Nielsen FH. Metabolic responses of postmenopausal women to supplemental dietary boron and aluminum during usual and low magnesium intake: boron, calcium, and magnesium absorption and retention and blood mineral concentrations. *Am J Clin Nutr* 1997;65:803–813.
15. Nielsen FH, Penland JG. Boron deprivation alters rat behaviour and brain mineral composition differently when fish oil instead of safflower oil is the diet fat source. *Nutr Neurosci* 2006;9:105–112.

16. Fort DJ, Stover EL, Strong PL, Murray FJ, Keen CL. Chronic feeding of a low boron diet adversely affects reproduction and development in *Xenopus laevis*. *J Nutr* 1999;129:2055–2060.
17. Fort DJ, Rogers RL, McLaughlin DW, Sellers CM, Schlekot CL. Impact of boron deficiency on *Xenopus laevis*. A summary of biological effects and potential biochemical roles. *Biol Trace Elem Res* 2002;90:117–142.
18. Rowe RI, Eckhert CD. Boron is required for zebrafish embryogenesis. *J Exp Biol* 1999;202:1649–1654.
19. Eckhert CD, Rowe RI. Embryonic dysplasia and adult retinal dystrophy in boron-deficient zebrafish. *J Trace Elem Exp Med* 1999;12:213–219.
20. Lanoue L, Strong PL, Keen CL. Adverse effects of a low boron environment on the preimplantation development of mouse embryos in vitro. *J Trace Elem Exp Med* 1999;12:235–250.
21. Nielsen FH, Stoecker B. Dietary boron and fish oil have desirable effects on vertebral microarchitecture and strength. *FASEB J* 2006;20:A561.
22. Gorustovich AA, Steimetz T, Nielsen FH, Guglielmotti MB. A histomorphometric study of alveolar bone healing in rats fed a boron-deficient diet. *FASEB J* 2006;20:A24.
23. Gorustovich AA, Steimetz T, Nielsen FH, Guglielmotti MB. A histomorphometric study of alveolar bone modeling and remodeling in mice fed a boron-deficient diet. *FASEB J* 2006;20:A195.
24. Nielsen FH, Stoecker BJ, Penland JG. Boron as a dietary factor for bone microarchitecture and central nervous system function. In: Xu F, Goldbach HE, Brown PH, Bell RW, Fujiwara T, Hunt CD, Goldberg S, Shi L, eds. *Advances in Plant and Animal Boron Nutrition*. Dordrecht, The Netherlands: Springer; 2007:277–290.
25. Gorustovich AA, Steimetz T, Haro LA, Nielsen FH, Guglielmotti MB. A histomorphometric study of alveolar bone healing in rats fed a boron-deficient diet. *Anat Rec*: in press.
26. Gorustovich AA, Porto López JM, Guglielmotti MB, Cabrini RL. Biological performance of boron-modified bioactive glass particles implanted in rat tibia bone marrow. *Biomed Mater* 2006;1:100–105.
27. Nielsen FH. Dietary fat composition modifies the effect of boron on bone characteristics and plasma lipids in rats. *Bio-Factors* 2004;20:161–171.
28. Armstrong TA, Flowers WL, Spears JW, Nielsen FH. Long-term effects of boron supplementation on reproductive characteristics and bone mechanical properties in gilts. *J Anim Sci* 2002;80:154–161.
29. Fort DJ, Stover EL, Rogers RL, Copley HF, Morgan LA, Foster ER. Chronic boron or copper deficiency induces limb teratogenesis in *Xenopus*. *Biol Trace Elem Res* 2000;77:173–187.
30. Hegsted M, Keenan MJ, Siver F, Wozniak P. Effect of boron on vitamin D deficient rats. *Biol Trace Elem Res* 1991;28:243–255.
31. Bai Y, Hunt CD. Dietary boron enhances efficacy of cholecalciferol in broiler chicks. *J Trace Elem Exp Med* 1996;9:117–132.
32. Beattie JH, MacDonald A. Effect of boron on bone metabolism in rats. In: Momčilović B, ed. *Trace Elements in Man and Animals*. Zagreb: IMI; 1991:26.29–26.30.
33. Stoecker BJ, Nielsen FH. Dietary fatty acid composition, dietary boron, and ovariectomy affect bone strength and microarchitecture. *FASEB J* 2005;19:A57.
34. Nielsen FH, Gallagher SK, Johnson LK, Nielsen EJ. Boron enhances and mimics some effects of estrogen therapy in postmenopausal women. *J Trace Elem Exp Med* 1992;5:237–246.
35. Penland JG. Quantitative analysis of EEG effects following experimental marginal magnesium and boron deprivation. *Magnes Res* 1995;8:341–358.
36. Penland JG. The importance of boron nutrition for brain and psychological function. *Biol Trace Elem Res* 1998;66:299–317.
37. Penland JG, Eberhardt MJ. Effects of dietary boron and magnesium on brain function of mature male and female Long-Evans rats. *J Trace Elem Exp Med* 1993;6:53–64.
38. Hunt CD, Idso JP. Dietary boron as a physiological regulator of the normal inflammatory response: a review and current research progress. *J Trace Elem Exp Biol* 1999;12:221–233.
39. Armstrong TA, Spears JW, Lloyd KE. Inflammatory response, growth, and thyroid hormone concentrations are affected by long-term boron supplementation in gilts. *J Anim Sci* 2001;79:1549–1556.
40. Bai Y, Hunt CD, Newman SM Jr. Dietary boron increases serum antibody (IgG and IgM) concentrations in rats immunized with human typhoid vaccine. *Proc ND Acad Sci* 1997;51:81.
41. Bourgeois A-C, Scott ME, Sabally K, Koski KG. Low dietary boron reduces parasite (Nematoda) survival and alters cytokine profiles but the infection modifies liver minerals in mice. *J Nutr* 2007;137:2080–2086.
42. Armstrong TA, Spears JW. Effect of boron supplementation of pig diets on the production of tumor necrosis factor- α and interferon- γ . *J Anim Sci* 2003;81:2552–2561.
43. Nielsen FH, Penland JG. Boron supplementation of perimenopausal women affects boron metabolism and indices associated with macromineral metabolism, hormonal status and immune function. *J Trace Elem Exp Med* 1999;12:251–261.
44. Kelley DS, Taylor PC, Nelson GJ, Mackey BE. Dietary docosahexaenoic acid and immunocompetence in young healthy men. *Lipids* 1998;33:559–566.
45. Kelly, DS, Taylor PC, Nelson GJ, Schmidt PC, Mackey BE, Kyle D. Effects of dietary arachidonic acid on human immune response. *Lipids* 1997;32:449–456.
46. Nielsen FH, Poellot R. Boron status affects differences in blood immune cell populations in rats fed diets containing fish oil or safflower oil. In: Anke M, Flachowsky G, Kisters K, et al., eds. *Macro and Trace Elements (Mengen- und Spurenelemente) Workshop 22*. Leipzig: Schubert-Verlag; 2004:959–964.
47. Nielsen FH. Does boron have an essential function similar to an omega-3 fatty acid? In: Anke M, Müller R, Schäfer U, Stoeppler M, eds. *Macro and Trace Elements (Mengen- und Spurenelemente) Workshop 21*. Leipzig: Schubert-Verlag; 2002:1238–1250.
48. Travers RL, Rennie GC, Newnham RE. Boron and arthritis: the results of a double-blind pilot study. *J Nutr Med* 1990;1:127–132.
49. Cui Y, Winton MI, Zhang ZF, Rainey C, Marshall J, De Kernion JB, Eckhert CD. Dietary boron intake and prostate cancer risk. *Oncol Rep* 2004;11:887–892.
50. Barranco WT, Eckhert CD. Boric acid inhibits human prostate cancer cell proliferation. *Cancer Lett* 2004;216:21–29.
51. Korkmaz M, Uzgören E, Bakirdere S, Aydin F, Ataman OY. Effects of dietary boron on cervical cytopathology and on micronucleus frequency in exfoliated buccal cells. *Environ Toxicol* 2007;22:17–25.
52. Touillaud MS, Pillow PC, Jakovljevic J, et al. Effect of dietary intake of phytoestrogens on estrogen receptor status in

- premenopausal women with breast cancer. *Nutr Cancer* 2005;51:162–169.
53. Bakken NA, Hunt CD. Dietary boron decreases peak pancreatic in situ insulin release in chicks and plasma insulin concentrations in rats regardless of vitamin D or magnesium status. *J Nutr* 2003;133:3577–3583.
 54. Fort DJ. Boron deficiency disables *Xenopus laevis* oocyte maturation events. *Biol Trace Elem Res* 2002;85:157–169.
 55. Goldbach HE, Wimmer MA, Chaumont F, et al. Rapid responses of plants to boron deprivation. Where are the links between boron's primary role and secondary reactions? In: Goldbach HE, Rerkasem B, Wimmer MA, Brown PH, Thellier M, Bell RW, eds. *Boron in Plant and Animal Nutrition*. New York, Kluwer Academic/Plenum Publishers; 2002:167–180.
 56. García-González M, Mateo P, Bonilla I. Boron protection for O₂ diffusion in heterocysts of *Anabaena* sp. PCC 7119. *Plant Physiol* 1988;87:785–789.
 57. Park M, Li Q, Shcheynikov N, Zeng W, Muallem S. NaBC1 is a ubiquitous electrogenic Na⁺-coupled borate transporter essential for cellular boron homeostasis and cell growth and proliferation. *Mol Cell* 2004;16:331–341.
 58. Shin K-W, Kiyohara H, Matsumoto T, Yamada H. Rhamnoglacturonan II from the leaves of *Panax ginseng* C.A. Meyer as a macrophage Fc receptor expression-enhancing polysaccharide. *Carbohydrate Res* 1998;307:97–106.
 59. Ralston NVC, Hunt CD. Diadenosine phosphates and S-adenosylmethionine: novel boron binding biomolecules detected by capillary electrophoresis. *Biochim Biophys Acta* 2001;1527:20–30.
 60. Chen X, Schauder S, Potier N, et al. Structural identification of a bacterial quorum-sensing signal containing boron. *Nature* 2002;415:545–549.
 61. Nielsen FH. Evidence for the nutritional essentiality of boron. *J Trace Elem Exp Med* 1996;9:215–229.
 62. Nielsen FH, Penland JG, Newman SM Jr. Dietary boron modifies the effect of changing dietary fatty acid composition on rat behavior and eye mitochondrial morphology. *FASEB J* 2004;18:A491.
 63. World Health Organization. Boron. In: *Trace Elements in Human Nutrition and Health*. Geneva: World Health Organization; 1996:175–179.
 64. Rainey CJ, Nyquist LA, Christensen RE, Strong PL, Culver BD, Coughlin JR. Daily boron intake from the American diet. *J Am Diet Assoc* 1999;99:335–340.
 65. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc*. Washington, DC: National Academy Press; 2001:618–619.
 66. Peng X, Lingxia Z, Schrauzer GN, Xiong G. Selenium, boron, and germanium deficiency in the etiology of Kashin-Beck disease. *Biol Trace Elem Res* 2000;77:193–197.
 67. Fang W, Wu P, Hu R, Huang Z. Environmental Se-Mo-B deficiency and its possible effects on crops and Keshan-Beck disease (KBD) in the Chousang area, Yao County, Shaanxi Province, China. *Environ Geochem Health* 2003;25:267–280.
 68. Havercroft JM, Ward NI. Boron and other elements in relation to rheumatoid arthritis. In: Momčilović B, ed. *Trace Elements in Man and Animals 7*. Zagreb: IMI; 1991:8.2–8.3.
 69. Beattie JH, Peace HS. The influence of a low-boron diet and boron supplementation on bone, major mineral and sex steroid metabolism in postmenopausal women. *Brit J Nutr* 1993;69:871–884.
 70. Nielsen FH. The alteration of magnesium, calcium and phosphorus metabolism by dietary magnesium deprivation in postmenopausal women is not affected by dietary boron deprivation. *Magnes Res* 2004;17:197–210.