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Growing Evidence for Human Health Benefits of Boron

Forrest H. Nielsen, PhD[1] and Susan L. Meacham, PhD[2]

Abstract

Growing evidence from a variety of experimental models shows that boron is a bioactive and beneficial (perhaps essential) element for humans. Reported beneficial actions of boron include arthritis alleviation or risk reduction, bone growth and maintenance, central nervous system function, cancer risk reduction, hormone facilitation, and immune response, inflammation, and oxidative stress modulation. The diverse effects of boron indicate that it influences the formation and/or activity of an entity that is involved in many biochemical processes. Formation of boroesters with the ribose moiety of compounds involved in numerous reactions, such as S-adenosylmethionine and oxidized nicotinamide adenine dinucleotide (NAD^+) might be the reason for boron bioactivity. Both animal and human data suggest that boron intakes should be >1.0 mg/d. Many people consume less than this amount. Thus, a low boron intake should be considered a health concern, which can be prevented by diets rich in fruits, vegetables, nuts, and pulses.

Keywords

boron nutrition, action mechanisms, intakes, S-adenosylmethionine, NAD, boroesters, ribose

Boron is widely distributed in nature and always found bound to oxygen. The ancient Egyptians have been credited with using boron compounds for mummification and in medicinal applications. However, the first conclusive evidence for the use of borax ($Na_2B_4O_7{\cdot}10H_2O$) for medicinal purposes dates from the 8th century in Mecca and Medina.[1] The presence of boron in plants has been known since 1857.[2] In the 1870s, it was discovered that sodium borate and boric acid could be used to preserve foods.[3] For about the next 50 years, borate addition was considered one of the best methods for preserving and 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 World War II. However, as early as 1902, German and American scientists began to question whether large amounts of borates in foods were innocuous. In 1904, Wiley[4] reported that boric acid in doses greater than 500 mg/d (77 mg boron per day) for 50 days resulted in disturbances in appetite, digestion, and health in human volunteers and concluded that boric acid at 4000 mg/d (699 mg boron per day) was the limit beyond which a harm to humans would occur. Subsequent to his report, the opinion that boron posed a risk to health grew. By the 1950s, boron as a food preservative was essentially forbidden throughout the world.

In the 1920s, boron was found to be an essential nutrient for plants.[5,6] Over the next 20 years, several unsuccessful attempts at showing boron essentiality in higher animals were made. This resulted in generations of students in nutrition being taught that boron was a unique element because it was essential for plants but not for higher animals and humans. In 1981, 2 reports appeared that suggested that boron could have nutritional benefits. Newnham[7] suggested that boron could alleviate arthritic symptoms, and Hunt and Nielsen[8] found that boron deprivation exacerbated gross bone abnormalities in chicks fed marginal amounts of vitamin D. Since then, an increasing number of reports have indicated that boron is a beneficial bioactive (if not essential) trace element for humans.

Boron Essentiality

Boron has been shown to be essential for the completion of the life cycle (ie, deficiency causes impaired growth, development, or maturation such that procreation is prevented) for organisms in all phylogenetic kingdoms. Higher animals that require boron to complete their life cycle are frogs[9,10] and zebrafish.[11,12] Boron-deprived male frogs exhibited atrophied testes, decreased sperm counts, and sperm dysmorphology. Female frogs exhibited atrophied ovaries and impaired oocyte

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maturation. Boron deprivation resulted in necrotic eggs and high mortality in embryos from frogs fed a boron-deficient diet. Boron deficiency also induced high mortality in zebrafish embryos. Although there are data suggesting that boron deprivation impairs early embryonic development in mice,[13] the critical experiment demonstrating that boron is essential for a mammal to complete the life cycle is lacking. However, boron has been shown to be a bioactive mineral element that has numerous beneficial actions in nutritional amounts for humans and higher animals.

Beneficial Actions

Arthritis

Since 1981,[7] occasional reports have appeared suggesting that boron can ameliorate or prevent arthritic symptoms. Based on limited observations in several countries, Newnham[14] reported that the occurrence of arthritis is negatively correlated with the amount of boron in the soil and in the food and water supply. In areas where daily boron intakes were typically $\leq$1.0 mg, the estimated incidence of arthritis ranged from 20% to 70%. In areas where daily boron intakes ranged from 3 to >10 mg, the estimated incidence of arthritis ranged from 0% to 10%. Newnham also stated that arthritic dogs, horses, and cattle given 3 mg of boron for every 25 kg of body weight generally showed improvement in 2 to 4 weeks. This observation apparently has not been confirmed by controlled experiments. Although the evidence in these early reports by Newnham[14] is weak, his suggestion that boron can help alleviate arthritic symptoms could have some merit. In a double-blind study conducted in Australia, 20 patients with confirmed osteoarthritis were given a placebo or a supplement providing 6 mg of boron daily for 8 weeks; 15 patients completed the study.[15] Of the 7 patients consuming the boron supplement, 5 reported improved subjective measures for their arthritic condition (eg, less pain on movement), whereas only 1 of 8 patients consuming the placebo reported an improvement in their arthritic condition. Shortly thereafter, it was reported that boron concentrations in bone and synovial fluid were lower in rheumatoid arthritis patients than in healthy controls.[16] A recent study of 20 patients with mild, moderate, or severe osteoarthritis also found that boron supplementation alleviated subjective measures of arthritis.[17] Patients with mild to moderate arthritis supplemented daily with 6 mg of boron as calcium fructoborate (a naturally occurring boron complex commonly found in fruits and vegetables) reported markedly reduced pain. By week 8, 80% of the test participants reduced or eliminated their use of painkillers. Joint rigidity essentially disappeared, and mobility was markedly increased at 8 weeks. Patients with severe arthritis, who were supplemented daily with 12 mg of boron as calcium fructoborate, exhibited a more subdued improvement in mobility and rigidity but still reported a significant reduction in the use of painkillers. These findings, however, are weakened by the nonblinding to treatment and lack of placebo controls. Interestingly, Keshan-Beck disease (characterized by degeneration of the articular cartilage between joints) has been associated with low boron concentrations in hair[18] and with deficient boron in soils and crops in China.[19]

Arthritic conditions are characterized by chronic inflammatory stress. Animal and cell culture studies have shown that boron can inhibit inflammatory stress such as that found in arthritic conditions. The incidence of severe paw swelling in rats following an intradermal injection of *Mycobacterium butyricum* to induce arthritis was less in rats fed 2.1 mg/kg of boron in the diet compared with rats fed 0.1 mg/kg in the diet.[20] In another study, a 20-mg/kg boron diet compared with a 0.2-mg/kg boron diet significantly decreased the incidence of arthritis 12 days postinjection with *M tuberculosis* to induce arthritis in rats.[21] Supplementing 5 mg/kg boron to a diet containing about 2 mg/kg boron decreased the localized swelling response induced by an intradermal injection of phytohemagglutinin in pigs.[22] The boron-supplemented pigs also had increased serum concentrations of the inflammatory cytokine, tumor necrosis factor-α.

In vitro studies also indicate that boron can affect the production of inflammatory cytokines by cartilage cells and cells involved in the inflammatory response. Boron as boric acid was found to stimulate the synthesis and release of tumor necrosis factor-α by chick embryo cartilage[23] and fibroblasts.[24] Recently, it was found that calcium fructoborate increased tumor necrosis factor-α protein in the culture media of RAW 264.7 macrophages stimulated by lipopolysaccharide.[25] The production and release of interleukin-1β and interleukin-6 were decreased by the stimulated macrophages cultured with calcium fructoborate. In contrast to the tumor necrosis factor-α findings above, Cao et al[26] reported that boric acid inhibited the lipopolysaccharide-induced tumor necrosis factor-α formation in cultured THP-1 monocytes.

A carefully controlled study of the effect of boron on objective indicators of arthritic symptoms with a sufficient number of human participants has not been reported. However, animal and cell culture studies suggest that a low boron status could increase the risk and severity of chronic inflammatory stress associated with arthritis. In addition, 2 experiments using subjective measures in a small number of participants and some limited epidemiological findings suggest that a boron intake higher than 1.0 mg/d could decrease the risk and severity of arthritic symptoms in humans. These provocative findings indicate that more studies should be done to determine whether boron supplementation has therapeutic value for some individuals at risk for or who have arthritis.

Bone Growth and Maintenance

Considerable evidence exists to support the contention that boron has a beneficial (if not an essential) function, influencing especially trabecular and alveolar bone growth and maintenance. Early findings indicating that boron deprivation was detrimental to bone growth independent of another stressor affecting bone health included decreased maturation of the bone growth plate in chicks[27] and induced limb teratogenesis

in frogs.[10] More recently, microcomputed tomography of the fourth lumbar vertebra found that boron deprivation (0.1 vs 3 mg/kg diet) 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) in rats.[28] Boron deprivation (0.07 mg/kg diet vs 3 mg/kg diet) in rats has also been shown to decrease alveolar bone (primary support structure for teeth) repair, which is initiated immediately after tooth extraction.[29] Histological examination revealed that boron deprivation decreased osteoblast surface and increased quiescent bone-forming surface in the alveolus. In addition, boron deprivation without tooth extraction impaired alveolar bone formation. Boron deprivation (0.07 mg/kg diet vs 3 mg/kg diet) for 9 weeks in mice decreased osteoblast surface and increased bone-forming surface in both the lingual and buccal side of the periodontal alveolar bone.[30] Boron supplementation also has been found to stimulate dental bone formation in rabbits[31] and increase mineralized nodule formation by cultured osteoblasts (MC3t3-E1).[32] Bioactive glasses have been modified to contain boron; this modification enhanced bone formation by the glasses,[33,34] which are used for bone tissue engineering and in situ bone tissue regeneration. In addition to adversely affecting bone, boron deprivation reduced enamel thickness (hypoplasia) in maturing dental enamel of rats.[35]

The changes in bone structure and formation induced by boron deprivation apparently affect bone strength and could increase the risk of osteoporosis. Boron deprivation decreased bone strength variables determined by a 3-point bending test of femurs from pigs[36,37] and rats.[28,38] Boron supplementation was found to increase mean trabecular density and thickness, trabecular bone volume, and cortical bone volume of femurs from rats with retinoic-induced osteoporosis.[39] Calcium fructoborate incorporated into margarine was found to improve bone density in 66 of 100 patients with osteoporosis.[40] As a result, it was concluded that calcium fructoborate could be a good adjuvant in the treatment of osteoporosis.

Brain Function

Findings showing that nutritional intakes of boron have beneficial effects on the central nervous system are more limited than those showing similar effects on the bone. However, the studies are among the most supportive of the suggestion that boron is a beneficial bioactive element for humans. Under well-controlled dietary conditions, boron supplementation after deprivation resulted in electroencephalograms indicative of improved behavior activation (eg, less drowsiness) and mental alertness, improved psychomotor skills of motor speed and dexterity, and improved cognitive processes of attention and short-term memory in older men and women.[41,42] Animal findings support the suggestion that boron is beneficial to brain function. Early studies found that boron deprivation affected brain electrical activity in rats in a manner similar to nonspecific malnutrition and heavy-metal toxicity.[43] More recently, it was found that boron deprivation alters rat behavior differently when dietary fat was supplied as fish oil instead of safflower oil.[44] Boron-deprived rats were less active than boron-supplemented rats when fed the diet with 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 less-active responses of boron-deprived rats. Boron-deficient zebrafish developed photophobia, which apparently was caused by photoreceptor dystrophy.[12]

Cancer

After an epidemiological study found an inverse association between dietary boron and prostate cancer,[45] Barranco and Eckhert initiated studies showing that boric acid completely inhibited the growth of the cultured prostate cancer cells, DU-145.[46-48] Subsequently, Carper et al[49] found that variable, often dose-dependent, amounts of boron gave responses indicating controlled apoptosis as opposed to a toxic or cytotoxic effect on DU-145, PC-3, and LNCaP-cultured prostate cells. Their initial studies found that 1 mmol/ L boric acid markedly inhibited growth of DU-145 cells, moderately inhibited growth of cultured LNCaP cells, and had a muted effect on growth of cultured PC-3 cells. Boron analogs such as phenylboronic acid and hydroxymethylphenylboronic acid also had similar inhibitory effects on growth that were consistent with those on growth of cancer cells in vitro reported by others using boric acid.[46,50] Boric acid at 1 mmol/ L also was found to inhibit growth of breast cancer cells in vitro.[51] Cultured SK-BR-3 and ZR-75-1 breast cells were only partially inhibited—an effect that was less than that with cultured DU-145 prostate cells. However, an apoptotic response occurred in cultured ZR-75-1 cells after 7 days of exposure to either boric acid or phenylboronic acid. Caspase 3 activities confirmed apoptotic, or programmed death, rather than a cytotoxic or necrotic death induced by the boron compounds. In contrast to $MgCl_2$, which stimulated cell attachment, boric acid and phenylboronic acid inhibited cell attachment.[51] Phenylboronic acid induced a dose-dependent block in the S-phase of the cell cycle in the detached ZR-75-A cells.

Changes in focal adhesion kinase were targeted as a possible mechanism of action through which boric acid induced apoptosis in both cultured breast and cultured prostate cancer cells. Focal adhesion kinase is overexpressed in several human cancer cell lines and is essential in the integrin-mediated signal transduction pathway; it participates in cell migration, angiogenesis, and inflammation/wound healing. Through phosphorylation reactions, focal adhesion kinase conformation changes elicit both intracellular and extracellular responses that suppress apoptosis and promote cell migration. A 4-fold reduction in phosphorylated focal adhesion kinase with concurrent increased caspase-3 occurred with boric acid treatment, which indicated apoptotic activity in the cancer cells.[52]

It should be noted that boron has been associated with other forms of cancer. A study of cervical smears from 472 women

with a high mean boron intake (8.41 mg/d) and 587 with marginal mean boron intake (1.26 mg/d) found 15 cases of cytopathological indications of cervical cancer in boron-low women and none in the boron-high women.[53] In a study of 763 women with lung cancer and 838 matched healthy controls, boron intake was inversely associated with the incidence of cancer; odds increased substantially if the women were not on hormone replacement therapy.[54]

Hormone Facilitator

Numerous studies indicate that boron intake affects the presence or function of hormones, including vitamin D, estrogen, thyroid hormone, insulin, and progesterone. The seminal finding indicating that boron is a bioactive beneficial element in nutritional amounts was that boron deprivation exacerbated gross bone abnormalities in chicks fed marginal amounts of vitamin D.[8] Hunt[55] found that boron deprivation exacerbated the distortion of marrow sprouts (location of calcified scaffold erosion and new bone formation), increased the number of osteoclasts within the marrow sprouts of the proximal tibial epiphyseal plate, and delayed initiation of cartilage calcification induced by marginal vitamin D in the chick. Subsequently, it was found that boron deprivation exacerbated marginal vitamin D deficiency–induced decreased calcium and phosphorus absorption and balance in rats,[56] increased plasma glucose and triglycerides in chicks,[27] and decreased growth and femur calcium concentrations in chicks.[57] Boron supplementation also has been found to increase plasma 1, 25-OH_2-vitamin D concentrations in rats.[58] In older men and women, boron supplementation (3 mg/d) after 63 days of boron deprivation (0.25 mg/d) increased serum 25-OH-vitamin D concentrations.[59] These findings suggest that boron could be beneficial to people with marginal vitamin D status, especially those living in areas where winter months provide minimal amounts of ultraviolet light for the synthesis of vitamin D in skin.

Boron has been shown to increase the efficacy of estrogen supplementation in both rats and humans. In ovariectomized rats fed an AIN-76 diet (high in sugar and oils that cause oxidative stress) containing 0.4 mg/kg boron, the addition of boron to the diet (5 mg/kg) significantly increased the beneficial effect of 17β-estradiol supplementation on trabecular bone volume fraction, bone growth plate density, and trabecular separation.[60] The combination of boron and 17β-estradiol versus either of these alone markedly improved the absorption of calcium, phosphorus, and magnesium and the retention of calcium and magnesium.[61] In postmenopausal women, the increases in serum 17β-estradiol and plasma copper induced by estrogen therapy were significantly higher when the women consumed 3.25 mg/d boron instead of 0.25 mg/d.[62] The higher boron intake enhanced the effect of estrogen therapy on serum triglyceride and immunoreactive ceruloplasmin concentrations. Boron intake also had a positive influence on the association between reduced lung cancer risk and hormone replacement therapy.[54] Women who consumed a diet low in boron and did not use hormone replacement therapy had substantially increased odds for lung cancer risk.

Boron also apparently influences thyroid hormone metabolism. Boron deprivation decreased the rate of tail resorption in larvae during their development into frogs. Addition of 100 fg thyroxine/L of medium, a known enhancer of tail absorption, reversed the delayed tail absorption.[10] In pigs, supplementing a low-boron diet (1-2 mg/kg) with 5 mg/kg boron during the nursery and growth stages decreased serum triiodothyronine and thyroxine.[63] Boron supplementation (2.5 mg/d) for 90 days decreased serum triiodothyronine in perimenopausal women after consuming a placebo for 90 days.[64]

Limited evidence suggests that boron can facilitate insulin action. Boron supplementation (2 mg/kg diet) of rats fed a boron-deficient diet (0.2 mg/kg diet) reduced plasma insulin but did not change plasma glucose concentrations.[65] Peak insulin release from the isolated, perfused pancreas of boron-deprived chicks was almost 75% higher than that from the pancreas of boron-supplemented chicks; the difference was especially noticeable when the perfusate was supplemented with glucose. An effect on insulin utilization could be the basis for the observation that boron deprivation induced a modest but significantly increased fasting serum glucose concentration in older men and women fed a low-magnesium, marginal copper diet.[66]

Boron was found to facilitate progesterone action in frog development. Incomplete frog oocyte maturation caused by boron deficiency could not be induced by the administration of exogenous progesterone.[67] Progesterone successfully induced germinal vesicle breakdown in oocytes from females fed a boron-supplemented diet.

Immune Response, Inflammation, and Oxidative Stress

In addition to the effects on inflammation described in the arthritis section above, other reports indicate that boron can affect the immune response, the populations of blood cells involved in the inflammatory response, and reactive oxygen species metabolism occurring with chronic inflammatory stress or the acute inflammatory response. Animal studies include the finding that supplementing 3 mg/kg boron to boron-deficient (0.2 mg/kg) diet more than doubled the serum total antibody concentrations in response to human typhoid vaccine injection in rats.[68] In mice, boron deprivation downregulated 30 of 31 cytokines or chemokines associated with the inflammatory response 6 days postprimary infection with the nematode *Heligmosomoides bakeri*.[69] An opposite pattern was found, especially 21 days postchallenge; mice consuming low and marginally boron-deficient diets had >100% increases in 23 of the 31 cytokines or chemokines.

Animal studies showing that boron can affect blood cell populations include one in which rats were fed diets where the fat source was fish oil (high in anti-inflammatory n-3 fatty acids) or safflower oil (high in n-6 fatty acids).[70] Compared with safflower oil, fish oil increased white blood cell numbers,

with most of the increase in the lymphocyte fraction, in boron-supplemented (3 mg/g diet) but not in boron-deprived (0.1 mg/g diet) rats. Fish oil instead of safflower oil increased monocyte and basophil numbers in boron-deprived but not in boron-supplemented rats. In another study, boron supplemented (2.0 mg/kg diet) rats had lower circulating concentrations of natural killer cells and CD8a+/CD4− cells than did boron-deficient (0.1 mg/kg diet) rats after injection with an antigen (*M butyricum* in mineral oil).[20]

One human study found that perimenopausal women excreting an average of 1.1 and 3.0 mg/d boron during placebo and boron supplementation periods, respectively, had increased white blood cell numbers, an increased percentage of neutrophils, and a decreased percentage of lymphocytes during the boron supplementation period.[64]

Activation of neutrophils and phagocytes during the inflammation process results in the production of reactive oxygen species such as superoxide, hydrogen peroxide, and the hydroxyl radical that are used for microbicidal purposes. Excess reactive oxygen species are destroyed in reactions involving glutathione, superoxide dismutase, and catalase. Evidence exists indicating that boron status can affect the destruction of reactive oxygen species. Boron supplementation (3.0 mg/d) significantly increased erythrocyte superoxide dismutase concentration in boron-deprived (0.25 mg/d) men and women.[59] Low doses (eg, 5 mg/L) of boron were found to support antioxidant enzyme activities, including superoxide dismutase and catalase, in human blood cultures.[71] Calcium fructoborate has been found to decrease the intracellular production or amount of superoxide ions in cultured cells exposed to oxidative stress.[40] Findings in an experiment with cultured THP-1 monocytes suggested that boron can limit inflammatory injury (lipopolysaccharide-induced tumor necrosis factor-α formation) even in the presence of glutathione deficiency.[26]

Related to a possible influence of boron on the response to infection is that 3 of the limited number of known natural biomolecules containing boron are antibiotics. These are boromycin from a strain of *Streptomyces antibioticus*,[72] tartrolon B produced by the myxobacterium *Sorangium cellulosum*,[73] and aplasmomycin produced by *Streptomyces griseus*.[74]

Possible Mechanisms of Actions

Biochemistry of Boron

The diverse responses reported for apparently deficient intakes of boron have made it difficult to identify a primary mechanism responsible for its beneficial bioactivity. The wide range of responses probably is secondary to boron influencing a cell signaling system or the formation and/or activity of an entity that is involved in many biochemical processes. The biochemistry of boron gives some clues about the possible basis for its bioactivity.

Boron biochemistry is essentially that of boric acid. Boric acid acts as a Lewis acid and accepts an electron pair from a base (H_2O) to form tetracovalent compounds such as $B(OH)_4^-$. Thus, the reaction

$$B(OH)_3 + H_2O \leftrightarrow B(OH)_4^- + H^+.$$

At the pH of blood (7.4) this reaction results in a dilute aqueous solution composed of $B(OH)_3$ (boric acid) and $B(OH)_4^-$ (borate). Because the pK_a of boric acid is 9.25, the abundance of these 2 species in blood should be 98.4% and 1.6%, respectively. Boric acid forms ester complexes with hydroxyl groups of organic compounds; this preferably occurs when the hydroxyl groups are adjacent and in *cis* orientation. This property results in boron as boric acid forming complexes with several biologically important sugars, including ribose. The fact that borate can stabilize ribose has given support to the speculation that early life on Earth was one in which RNA was the only genetically encoded component of biological catalysts.[75] Without boron, RNA would have been unlikely to form spontaneously in prebiotic conditions because its ribose component would have decomposed under the harsh conditions of early Earth.

Hypothesized Boron Mechanisms of Action Involving Adenosine

Ribose is a component of adenosine. The diverse actions of boron could occur through its reactions with biomolecules containing adenosine or formed from adenosine precursors, including those shown in Figure 1. S-adenosylmethionine and diadenosine phosphates have higher affinities for boron than any other recognized boron ligands in animal tissues.[76] Diadenosine phosphates are present in all animal cells and function as signal nucleotides associated with neuronal response. As shown in Figure 2, S-adenosylmethionine is synthesized from adenosine triphosphate and methionine; it is one of the most frequently used enzyme substrates in the body.[77] About 95% of S-adenosylmethionine is used in methylation reactions, which influence the activity of DNA, RNA, proteins, phospholipids, hormones, and transmitters. The methylation reactions result in the formation of S-adenosylhomocysteine, which can be hydrolyzed into homocysteine.[78] High circulating homocysteine and depleted S-adenosylmethionine have been implicated in many of the disorders that can be affected by nutritional intakes of boron, including arthritis, osteoporosis, cancer, diabetes, and impaired brain function. Support for the hypothesis that boron bioactivity could be associated with S-adenosylmethionine are the findings that plasma homocysteine increased and liver S-adenosylmethionine and S-adenosylhomocysteine decreased in boron-deprived (0.05 to 0.15 mg/kg diet) compared with boron-supplemented (3 mg/kg diet) rats.[79] Additional support includes the finding that the bacterial quorum-sensing signal molecule, auto-inducer-2, is a furanosyl borate ester synthesized from S-adenosylmethionine.[80] Quorum sensing is the cell-to-cell communication between bacteria accomplished through the exchange of extracellular signaling molecules (autoinducers).

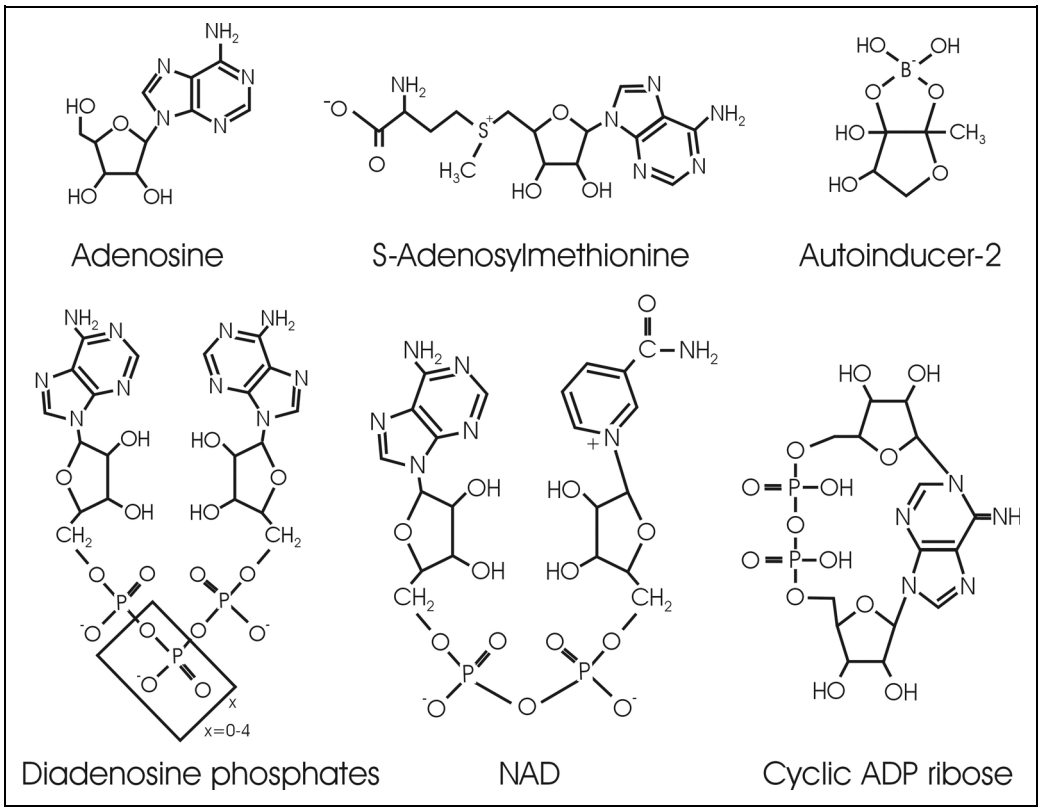

Figure 1. Ribose-containing biomolecules that bind boron

Boron also strongly binds oxidized nicotinamide adenine dinucleotide (NAD^+) and thus could influence reactions in which it is involved.[76] One role of extracellular NAD^+ is binding to the plasma membrane receptor CD38, which is an adenosine diphosphate (ADP)-ribosyl cyclase that converts NAD^+ to cyclic ADP ribose. Cyclic ADP ribose is released intracellularly and binds to the ryandodine receptor, which results in the release of Ca^{2+} from the endoplasmic reticulum. Cell culture studies show that boric acid binds to and is a reversible inhibitor of cyclic ADP ribose.[81,82] Boric acid in concentrations that can be found in blood decreased Ca^{2+} release from ryanodine receptor–sensitive stores.[82] Thus, Eckhert[83] has hypothesized that boron could be bioactive through binding NAD^+ and/or cyclic ADP ribose and inhibiting the release of Ca^{2+}. Ca^{2+} is a signal ion for many processes in which boron has been shown to have an effect, including insulin release, bone formation, immune response, and brain function.

Hypothesized Mechanism of Actions Involving Cell Membrane Function, Integrity, and Signaling

Boron can also be bioactive through forming diester borate complexes with phosphoinositides, glycoproteins, and glycolipids, which contain *cis*-hydroxyl groups in membranes. Diester borate polyl complexes could act as calcium chelators and/or redox metabolism modifiers[84] that affect membrane integrity and function.[85] A diester borate complex in membranes could be the molecular species that controls the transmembrane partitioning of boron.[86] Transporters across the cell membrane have been identified for plants,[87] yeast,[88] and animal cells.[89] The finding that the borate transporter NaBC1, which apparently is essential for boron homeostasis in animal cells, conducts Na^+ and OH^- across cell membranes in the absence of boron,[89] supports the suggestion that boron affects the transduction of regulatory or signaling ions across cell membranes. It has been hypothesized that a primary essential role for boron in plants, perhaps involving an interplay between boron and calcium, is at the cell membrane level that affects signaling events.[90] Plant findings also have led to the hypothesis that boron could act as a cellular signal that interacts with transcription factors and thus affects the expression of some genes.[91] These hypotheses suggest that boron could influence cell differentiation, organogenesis, and embryogenesis.[92,93] Support for this suggestion comes from boron deprivation findings from frog, zebrafish, and bacteria studies. In the boron-deprived *Xenopus* model, abnormal gastrulation is characterized by bleeding yolk and exogastrulation, which suggests disturbed cell membrane structure or function.[9,10] The most prevalent pathological changes before death of boron-deprived zebrafish during the zygote and cleavage periods were extensive membrane blebbing and extrusion of cytoplasm.[11,12] The changes occurred when cells were producing prodigious amounts of membranes, and they were consistent with membrane alterations reported for boron-deficient cyanobacteria.[94]

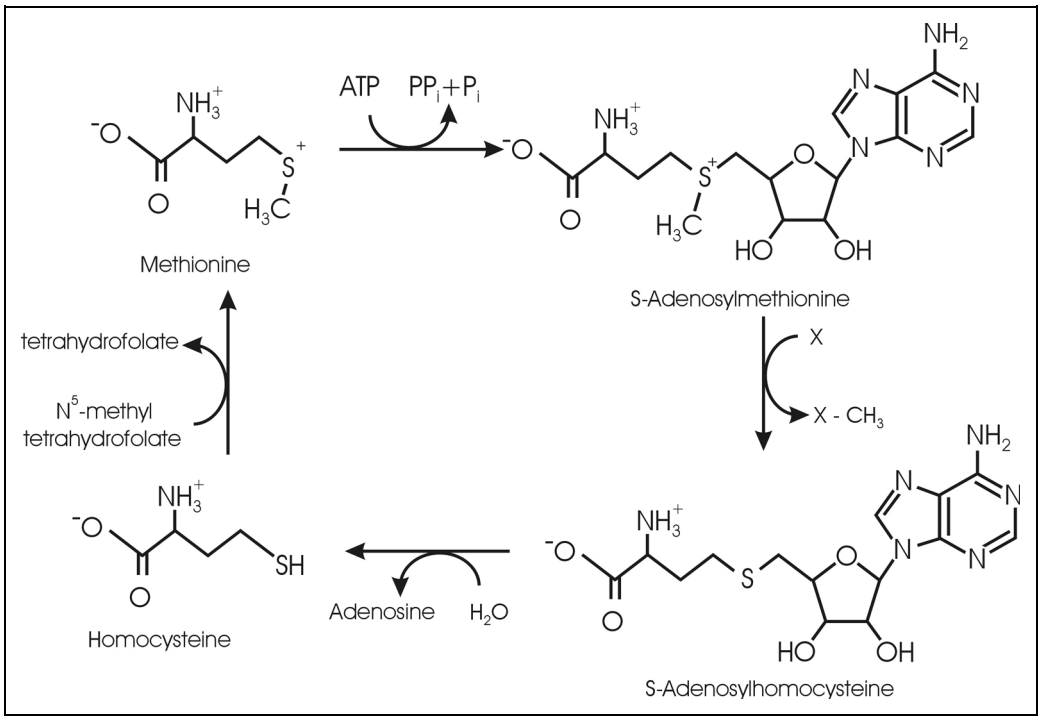

Figure 2. Pathway showing the formation of S-adenosylmethionine, S-adenosylhomocysteine, and homocysteine

Intakes That Affect Health

Nutritional

Both animal and human data were used by the World Health Organization (WHO)[95] to suggest that an acceptable safe range of population mean intakes of boron for adults could be 1 to 13 mg/d. This suggestion implies that intakes <1.0 mg/d is inadequate for optimal boron beneficial activity. The 1994-1996 Continuing Survey of Food Intakes by Individuals indicated that boron intakes ranged from a low of about 0.35 mg/d to a high of about 3.25 mg/d for adults.[96] The median intake for various age groups of adults ranged from 0.87 to 1.13 mg/ d. These figures suggest that a significant number of people consume less than desirable amounts of boron. Findings from a study involving 43 postmenopausal women in eastern North Dakota[64] also indicate a similar conclusion. Average urinary excretion of boron (a good indicator of intake) was <0.5 mg/d for 2 women and between 0.5 and 1.0 mg/d for 14 women. In human depletion–repletion experiments, participants responded to a 3 mg/d boron supplement after consuming a diet supplying only 0.2 to 0.4 mg/d boron for 63 days.[41,42.59,62] These findings indicate that usual intakes of boron above 1.0 mg/d would promote human health.

Safe Upper Level of Intake

Despite the large array of findings showing beneficial effects of boron in animal and human studies, the US Institute of Medicine Food and Nutrition Board[96] did not set an adequate intake level for boron. However, they set a tolerable upper intake level of 20 mg/d. The World Health Organization first suggested that 13 mg/d would be a safe upper intake level[95] but later increased this to 0.4 mg/kg body weight or about 28 mg/d for a 70-kg person.[97] The European Union established an upper intake level for total boron intake based on body weight that results in about 10 mg/d for adults.[98] Interestingly, they suggested 1.0 mg/L to be a safe drinking water standard for boron.[99] This resulted in considerable debate because in some regions in the world, boron concentrations are normally much higher than this. One study found that 10% of 600 drinking water sources had boron concentrations exceeding 1.0 mg/L in the European Union.[100] The World Health Organization first suggested 0.3 mg/L[101] then later 0.5 mg/L as a tolerable level for boron.[97] This increase was appropriate based on the finding that the mortality rate in northern France was significantly lower when drinking water contained >0.3 mg/L than when it contained <0.3 mg/L.[102] Moreover, the low upper intake levels set for drinking water seem inconsistent with the upper intake levels established throughout the world and with the lack of finding of adverse effects in areas of the world where the drinking water is high in boron. For example, Sayli and coworkers[103-106] found that high concentrations in drinking water, and consequently in food, in Turkey did not negatively affect health. In a population exposed to drinking water containing up to 29 mg/L boron and to boron mining and production, no adverse effects on health or fertility were found over 3 generations. In another study, no adverse effects were found in 66 men (mean age of 39 years) residing in a high boron area for 36 years who had a calculated boron excretion of 6.77 mg/L, which

indicated a high intake of boron. The drinking water in the area where they resided had boron concentrations that ranged from 2.05 to 29.00 mg/L, with a mean of 10.2 ± 4.1 mg/L. This level is 200 to 1000 times the typical values reported for most surface waters (0.01-0.05 mg/L).[107] The findings with drinking water containing high levels of boron and recent findings on the beneficial actions of boron suggest that relaxation of current safe drinking water standards for boron might be appropriate.

Assessment of Boron in the Diet

The preceding discussion indicates that people consuming <1 mg/d will benefit from increased intakes of boron and that it would be best not to exceed intakes above the upper intake level (20 mg/d in the United States and Canada). Assessing human diets to ascertain whether they contain boron in the range of 1 to 20 mg/d requires a thorough analysis of foods, water, and supplements. Several reports have given the boron content of commonly consumed foods and, consequently, an estimated daily dietary intake. The major reports have been by Hunt et al,[108] Anderson and Cunningham,[109] and Hunt and Meacham[110] who used different analytical and digestion techniques to determine boron levels. Rainey and Nyquist[111] used literature boron values for foods to estimate daily dietary boron intakes in several countries. Foods of plant origin, especially fruits, leafy vegetables, nuts, and legumes, are rich in boron, as are wine, cider, and beer. Some of the highest boron concentrations (μg/g fresh weight) are found in avocado (14.3 ± 0.4), peanut butter (5.9 ± 0.2), prune juice (5.6 ± 0.0), chocolate powder (4.3 ± 0.4), wine (3.6 ± 0.0), grape juice (3.4 ± 0.0), and pecans (2.6 ± 0.1).[110] These values can vary based on the environment in which the foods are produced.

Improvements in boron assessment methods are needed to more accurately assess boron intakes throughout the world. Because boron analysis is expensive and time-consuming, quality analyses of its presence in food and supplements are limited. In addition, values obtained for foods before 1990 are questionable. At present, urinary excretion is often used as an indication of dietary boron intake. The most widely used method to determine nutrient intake is using values for foods whose intakes have been estimated by food diaries—usually 3-day food records. This determination usually involves software programs that use databases of food composition tables. For boron, this has resulted in some questionable boron intake estimations.

An example of misleading boron intakes comes from a study in which a popular computer software was used to estimate the boron intakes from a single set of diet records. The boron content was available for only 322 foods, or 1.2% of the 26 000 foods in the database. Moreover, boron values reported in the database erroneously used mg/g instead of μg/g of food, which resulted in the limited foods with boron values giving a much higher than expected boron intake and masking the fact that a very limited number of foods in the database had boron values.[112] In this study from which diet records were obtained, duplicate plate collections were obtained. This allowed for an actual boron determination in the diets that was compared with repeat software boron determinations over time as new versions of the software program were updated and released. The versions gave intakes of 4.5, 4.97, and 5.25 mg/d boron in comparison with the analytical determination of 1.2 mg/d. The software values were 3 to 4 times higher than values from other determinations of dietary boron intake.[112-115]

Dietary supplements are another complicating factor in assessing dietary boron intake. The US National Library of Medicine Dietary Supplements Labels Database reveals an increasing number of supplements with boron as a listed ingredient. In 2009, boron ranged from 0.07 to 3 mg/unit boron in 203 products; only 3 contained 3 mg/unit. One product showed a value of 60 mg/unit, but the issuer confirmed that this was a reporting error; the corrected value was 750 μg/15 mL unit for the liquid mineral supplement. In addition to supplements, other unexpected sources of boron can influence its dietary intake; examples include sea salts and chia seeds.

The preceding indicates that although assessment methods for boron are improving, estimates of boron status or dietary intake by using food records must be viewed with caution. Analytical determinations of all items (food, water, and supplements) over a period of time would be the most accurate method for assessing boron intake. Urinary boron excretion could be used to support the accuracy of a boron intake determination.

Summary and Conclusions

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. Boron apparently has diverse effects through influencing a cell signaling system or the formation and/or activity of an entity involved in many biochemical processes. Findings have shown that boron is needed to complete the life cycle of some higher animals; in nutritional amounts, it promotes bone health, brain function, and the immune or inflammatory response; alleviates or decreases the risk for arthritis; facilitates the action or utilization of several hormones; and is associated with decreased risk for some cancers. This suggests that boron intakes above 1 mg/d could help people ''live longer and better.'' Increased intakes of boron through consuming foods such as fruits, vegetables, nuts, and pulses should be recognized as a reasonable dietary recommendation.

Author Contributions

Forrest H. Nielsen was responsible for the overall preparation and final editing of the manuscript. Susan L. Meacham was responsible for writing the sections on cancer, intakes that affect health, and assessment of boron in the diet.

Declaration of Conflicting Interests

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