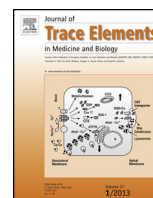




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## Review

# Update on human health effects of boron

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### ABSTRACT

In vitro, animal, and human experiments have shown that boron is a bioactive element in nutritional amounts that beneficially affects bone growth and central nervous system function, alleviates arthritic symptoms, facilitates hormone action and is associated with a reduced risk for some types of cancer. The diverse effects of boron suggest that it influences the formation and/or activity of substances that are involved in numerous biochemical processes. Several findings suggest that this influence is through the formation of boroesters in biomolecules containing *cis*-hydroxyl groups. These biomolecules include those that contain ribose (e.g., *S*-adenosylmethionine, diadenosine phosphates, and nicotinamide adenine dinucleotide). In addition, boron may form boroester complexes with phosphoinositides, glycoproteins, and glycolipids that affect cell membrane integrity and function. Both animal and human data indicate that an intake of less than 1.0 mg/day inhibits the health benefits of boron. Dietary surveys indicate such an intake is not rare. Thus, increasing boron intake by consuming a diet rich in fruits, vegetables, nuts and pulses should be recognized as a reasonable dietary recommendation to enhance health and well-being.

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### Introduction

Boron has been shown to be essential for the completion of the life cycle (deprivation causes impaired growth, development, or maturation such that procreation is prevented) for organisms in all phylogenetic kingdoms. In the animal kingdom, boron deprivation has been shown to adversely affect reproduction and embryo

development in the African clawed frog [1] and zebra fish [2]. Experiments have not been reported showing that boron deprivation interrupts the life cycle in mammals, or finding a specific biochemical function for boron. However, substantial evidence has been reported that indicates boron is a bioactive food component that is beneficial, if not required, for health and well-being. Recent findings continue to show that nutritional amounts of boron fed to animals and humans consuming a diet low in boron induce numerous biochemical and functional responses considered beneficial for bone growth and maintenance, brain function, and perhaps cancer risk reduction.

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## Boron and arthritis

Since 1981, occasional reports have appeared suggesting that boron can ameliorate or prevent arthritis. Animal studies have shown that boron can inhibit inflammatory responses to material injected to induce arthritic conditions [3,4]. In 1990, it was reported that 15 individuals with confirmed osteoarthritis completed a double-blind study in which they were given either a supplement of 6 mg boron or placebo daily for eight weeks [5]. Five of the seven subjects consuming the boron supplement reported improved subjective measures such as less pain on movement for their arthritic condition. Only one of eight subjects consuming the placebo reported improved subjective measures.

More recent studies suggesting that boron may ameliorate arthritic conditions includes a report [6] that a 6 mg/d boron supplement in the form of calcium fructoborate, a naturally occurring boron complex found in fruits and vegetables, alleviated subjective measures of mild, moderate, or severe osteoarthritis in 20 subjects. After eight weeks of supplementation, 80% of patients with mild or moderate osteoarthritis reported reduced or eliminated use of painkillers. In addition, joint rigidity essentially disappeared, and mobility was markedly increased. Patients with severe arthritis, who were supplemented daily with 12 mg boron as calcium fructoborate, had a more subdued improvement in mobility and rigidity, but did report a significant reduction in painkillers. The findings in this study, however, are weakened by the non-blinding to treatment and the lack of placebo controls. Subsequently, a double-blind, placebo-controlled pilot study was done to evaluate the effect of calcium fructoborate on systemic inflammation in middle-aged subjects with primary knee osteoarthritis [7]. The study was completed by 60 of 72 subjects in which groups of 15 were supplemented with a placebo or boron at 3, 6, or 12 mg/d as calcium fructoborate for 15 days. When all boron-supplemented subjects were grouped together, inflammatory stress biomarkers serum C-reactive protein, plasma fibrinogen and erythrocyte sedimentation rate were significantly improved compared to the placebo group. Surprisingly, the group given 3 mg boron/d exhibited the greatest improvement in plasma fibrinogen and serum C-reactive protein. These provocative findings need to be supported or confirmed by additional carefully controlled studies, preferably by other research groups. The studies should determine the effect of boron in other forms on objective indicators of arthritic symptoms and inflammatory stress in groups larger than 15 individuals to provide convincing evidence that increased boron intakes or supplementation would be of benefit for some individuals at risk for or who have arthritis.

## Boron and bone

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 [8] and induced limb teratogenesis in the African clawed frog [1]. Since those findings, considerable evidence has appeared to support the contention that boron has a beneficial effect on trabecular and alveolar bone growth and maintenance. Most of this evidence has come from animals and cell culture experiments.

When rats fed diets containing 0.1 mg boron/kg were compared to those fed 3.0 mg boron/kg diet, microcomputed tomography of the fourth lumbar vertebra revealed decreased bone volume fraction and trabecular thickness, and increased trabecular separation and structural model index (low values indicating a preferable more plate-like structure) [9]. Boron deprivation (0.07 vs. 3 mg/kg diet) in rats also has been shown to decrease alveolar bone

(primary support structure for teeth) repair that is initiated immediately after tooth extraction [10]. Boron deprivation decreased osteoblast surface and increased quiescent bone-forming surface in the alveolus. In addition, boron deprivation for nine weeks impaired alveolar bone formation without tooth extraction in mice [11]. Boron deprivation decreased osteoblast surface and increased bone-forming surface in both the lingual and buccal side of periodontal alveolar bone. Boron supplementation (3 mg/d for 10 or 20 days) also has been found to stimulate dental bone formation and increase bone mineral density in rabbits undergoing orthopedically expanded suture [12]. In contrast to alveolar bone, enamel mineralization was not affected by 14 days of boron deprivation (0.07 vs. 3 mg/kg diet) in rats aged 21 days, although enamel thickness was reduced (hypoplasia) [13].

Recent studies with bioactive glasses, which are used for bone tissue engineering and in situ bone tissue regeneration, provide supporting evidence that boron is beneficial for bone formation. Bone formation is enhanced when bioactive glasses are modified to contain boron [14–16]. Some of this enhancement might be caused by an effect on angiogenesis, which is critical for wound repair and tissue engineering. Borosilicate bioactive glass ionic dissolution products increased angiogenesis in quail embryos [17].

Cell culture studies also support the concept that boron is beneficial for bone formation and maintenance. Boron supplementation at 1 or 10 ng/mL compared to supplementation at 0 and 0.1 ng/mL increased mineralized nodule formation and mineralized tissue-associated mRNA expressions of type 1 collagen, osteopontin, bone sialoprotein, osteocalcin, and RunX by cultured osteoblasts (MC3T3-E1) [18]. In addition, the boron supplementation increased bone morphogenetic proteins 4, 6, and 7 levels.

The changes in bone structure and formation induced by boron deprivation might be a risk factor for osteoporosis. Six months of supplementation with calcium fructoborate (226 mg/d) incorporated into margarine was found to improve bone density in 66 of 100 patients with osteoporosis [19]. This finding resulted in the suggestion that calcium fructoborate may be a good adjuvant in the treatment of osteoporosis.

Although there is convincing evidence from animal and cell culture studies that boron is beneficial to bone growth and maintenance, the limited findings with humans will be an impediment to acceptance of this being a bioactive effect that would stimulate consideration for providing dietary guidance for boron. More studies determining the relationship between boron and bone health in humans are definitely needed.

## Boron and the central nervous system

Findings showing that nutritional intakes of boron have beneficial effects on the central nervous system are among the most supportive of the suggestion that boron is a beneficial trace element for humans. Under well-controlled dietary conditions, boron supplementation (3 mg/d) to older men and women after consuming diets providing about 0.25 mg boron/2000 kcal for about 63 days altered electroencephalograms (EEG) such that there was a shift toward less activity in the low frequencies and more activity in the high, dominant frequencies of the EEG spectrum [20,21]. A similar effect was found in rats [22]. Increased low-frequency activity is typical of states of reduced behavioral activation and has been associated with reduced performance in psychomotor tasks. Decreased high-frequency activity has been associated with impaired memory performance. Subjects supplemented with boron after deprivation exhibited improved psychomotor skills of motor speed and dexterity, and cognitive processes of attention and short term memory [20,21]. Since 1990s when these findings were found, there apparently have been no further studies involving the effect

of boron deprivation or supplementation on central nervous system function in humans. Recently, however, it was found that boron-deficient rats (0.1 mg/kg diet) were less active than boron-supplemented rats (3.0 mg/kg diet) rats. Boron deprivation reduced the number, distance, and time of horizontal movements, front entries, margin distance, and vertical breaks and jumps in a spontaneous activity evaluation [23]. Although this animal study provides support, another human study is needed to confirm that boron has a positive effect on central nervous system function before such an effect is likely to be used to provide dietary guidance for boron.

### Boron and cancer

One of the most recent suggested beneficial effects of boron is a reduced risk for some types of cancer. This suggested benefit was initiated by an epidemiological study that found an inverse association between dietary boron and prostate cancer [24]. Since then several studies have shown that boron inhibits the growth of some types of cultured prostate [25–27] and breast cancer cells [28], and human prostate adenocarcinoma tumors in nude mice [29]. Boron also has been inversely associated with cervical and lung cancers. A study of cervical smears from 472 women with a mean boron intake of 8.41 mg/d and 587 with a mean intake of 1.26 mg/d found 15 cases of cytopathological indications of cervical cancer in the boron-low women and none in the boron-high women [30]. In a study of 763 women with lung cancer and 838 matched healthy controls, boron intake was inversely associated with the incidence of lung cancer [31]. The odds increased substantially if the women were not on hormone replacement therapy.

### Boron and hormone facilitation

Numerous studies indicate that boron has beneficial effects on the functions of hormones, including vitamin D, estrogen, thyroid hormone, insulin, and progesterone. However, studies involving this beneficial effect have not been reported in the past ten years. Thus, a brief review of the older findings will be presented here to indicate that hormone facilitation may be a significant health benefit of boron.

The seminal finding indicating 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 [32]. These abnormalities included distortion of the marrow sprouts (location of calcified scaffold erosion and new bone formation), increased number of osteoclasts within the tibial epiphyseal plate marrow sprouts, and delayed initiation of cartilage calcification [33]. Subsequently, it was found that boron deprivation exacerbated marginal vitamin D deficiency-induced decreased calcium and phosphorus absorption in rats [34], increased plasma glucose and triglycerides in chicks [8], and decreased growth and femur calcium concentrations in chicks [35].

Boron also has been shown to increase efficacy of some steroid hormones. In ovariectomized rats fed a diet containing 0.4 mg/kg boron, supplemental 5 mg/kg boron significantly increased the beneficial effect of 17 $\beta$ -estradiol supplementation on trabecular bone volume fraction, bone growth plate density, and trabecular separation [36]. The combination of boron and 17 $\beta$ -estradiol vs. either of these alone markedly improved the absorption of calcium, phosphorus and magnesium, and the retention of calcium and magnesium [37]. In frogs, incomplete oocyte maturation caused by boron deficiency could not be induced by the administration of exogenous progesterone [38]. Progesterone successfully induced germinal vesicle breakdown in oocytes from females fed a boron-supplemented diet.

Limited evidence suggests that boron can facilitate insulin action. In rats fed a diet containing 0.2 mg/kg boron, a supplement of 2 mg/kg boron reduced plasma insulin but did not change plasma glucose concentrations [39]. Another finding was that peak insulin release from isolated perfused pancreas of boron-deprived chicks was almost 75% higher than from pancreas of boron-supplemented chicks [39]. The difference was especially noticeable when the perfusate was supplemented with glucose.

### Plausible boron mechanisms of action

The diverse responses reported for animals and humans deprived of boron have made it difficult to identify a primary mechanism for its possibly beneficial activity. The wide range of responses likely is secondary to boron influencing a cell signaling system and/or the formation and/or activity of entity that is involved in many biochemical processes.

A plausible mechanism of action may be indicated by the biochemistry of boron. Boric acid forms ester complexes with hydroxyl groups of organic compounds, which preferably occurs when the hydroxyl groups are adjacent and in a *cis* orientation. This property results in the formation of complexes with several biologically important sugars. These sugars include ribose, which is a component of adenosine. Recent findings suggest that the diverse beneficial effects of boron occur through affecting the presence or action of biomolecules containing adenosine or formed from adenosine precursors. These biomolecules include S-adenosylmethionine and diadenosine phosphates that have higher affinities for boron than any other recognized boron ligands in animal tissues [40]. Diadenosine phosphates are present in all animal cells and function as signal nucleotides involved with neuronal response. S-adenosylmethionine is one of the most frequently used enzyme substrates in the body [41]. 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.

Support for the hypothesis that boron bioactivity is through an effect on S-adenosylmethionine formation and/or utilization are the findings that plasma homocysteine increased and liver S-adenosylmethionine decreased in rats fed 0.05–0.15 mg/kg boron and compared to rats supplemented with 3 mg/kg diet [42]. 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. Further support for the hypothesis is that the bacterial quorum-sensing signal molecule, auto-inducer-2, is a furanosyl borate ester synthesized from S-adenosylmethionine [43]. Quorum sensing is the cell-to-cell communication between bacteria accomplished through the exchange of extracellular signaling molecules (auto-inducers).

Boron also strongly binds oxidized nicotinamide adenine dinucleotide (NAD<sup>+</sup>) [40] and thus might influence reactions in which it is involved. One role of extracellular NAD<sup>+</sup> is binding to the plasma membrane receptor CD38, an adenosine diphosphate ribosyl cyclase that converts NAD<sup>+</sup> to cyclic ADP ribose. Cyclic ADP ribose is released intracellularly and binds the ryanodine receptor, which induces the release of calcium ions from the endoplasmic reticulum. Cell culture studies show that boron binds to and is a reversible inhibitor of cyclic ADP ribose [44,45]. Boron in concentrations that are found in blood was found to decrease Ca<sup>2+</sup> release from ryanodine receptor-sensitive stores [45]. Thus, it has been hypothesized that boron is bioactive through binding NAD<sup>+</sup> and/or

cyclic ADP ribose and inhibiting the release of  $\text{Ca}^{2+}$ , which is a signal ion for many processes affected by boron, including insulin release, bone formation, immune response, and brain function.

Studies with plants have resulted in another suggested plausible mechanism of action for boron bioactivity. Boron might be bioactive through forming diester borate complexes with phosphoinositides, glycoproteins, and glycolipids in cellular membranes. Diester borate polyol complexes might act as calcium chelators and/or redox modifiers [46] that affect membrane integrity and function [47]. This modifying effect could alter the transduction of regulatory or signaling ions across membranes. Determination of such an effect in animals and humans has yet to be determined. However, the finding that the borate transporter NaBC1, which apparently is essential for boron homeostasis in animal cells, conducts  $\text{Na}^+$  and  $\text{OH}^-$  across cell membranes in the absence of boron [48], supports the suggestion that boron deprivation might affect the transduction of regulatory and signaling ions across cell membranes.

### Beneficial intakes of boron

Both animals and humans deprived of boron exhibit positive health benefits when provided with intakes of boron that may be achieved through consuming foods of plant origin. In human depletion–repletion experiments, participants responded to a 3 mg/d boron supplement after consuming a diet supplying only 0.2–0.4 mg boron/d for 63 days [21,22,49]. Extrapolations from animal experiments indicate that to achieve optimal benefits of boron, intakes  $>0.5$  mg/d are needed and that boron supplementation is unlikely to elicit a response in individuals consuming at least 1 mg boron/d [50]. Thus, if an adequate intake level is ever established for the health benefits of boron, it is likely to be between 0.5 and 1.0 mg/d.

In the United States, a survey conducted between 1994 and 1996 indicated boron intakes ranged from a low of 0.35 to a high of 3.25 mg/d for adults. The median intakes for various age groups of adults ranged from 0.87 to 1.13 mg/d [51]. Findings from a study involving 43 postmenopausal women in eastern North Dakota found that average urinary excretion of boron, which is a good indicator of dietary intake, was less than 0.5 mg/d for two women and between 0.5 and 1.0 mg/d for 14 women [52]. These findings suggest that a significant number of people could benefit through an increased intake of boron. Foods that would provide rich amounts of boron include fruits, leafy vegetables, nuts, and legumes. Beverages based on fruits and grains, such as wine, beer and cider also are good sources of boron.

### Safe intakes of boron

The U.S. Institute of Medicine, Food and Nutrition Board set a tolerable upper intake level of 20 mg/d for boron [51]. The World Health Organization first suggested that 13 mg/d would be a safe upper intake level [50] but later increased this to 0.4 mg/kg body weight or about 28 mg/d for a 70 kg person [53]. The European Union established an upper intake level for total boron intake based on body weight that equals about 10 mg/d for adults [54]. The finding that relatively high intakes of boron are needed to have an adverse effect is supported by reports of no adverse effects of high boron in drinking water in various places in the world. For example, in a Turkey population exposed to drinking water containing up to 29 mg/L boron and to boron mining and production, no adverse effects on health and fertility were found over three generations [55,56]. The preceding indicates that there is a wide window (10–20-fold) between boron intakes with possible adverse effects and the suggested beneficial intake of 1.0 mg/d.

### Conclusion

Recent findings augment prior substantial evidence indicating that boron in nutritional amounts and by plausible mechanism of actions has health benefits that may impact the risks for or severity of arthritis, osteoporosis or bone fractures, cancer, and impaired central nervous system function. Consideration should be given for providing dietary guidance for boron. If the science base is not considered requisite to set an adequate intake level, an appropriate action would include in dietary recommendations a statement that the consumption of foods resulting in a boron intake of 1.0 mg/d would assure its purported health benefits.

### Conflicts of interest

The author has no conflict of interests to declare.

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