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# Historical and recent aspects of boron in human and animal health

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## ABSTRACT

Evidence that boron is a beneficial bioactive trace element is substantial. The evidence has come from numerous laboratories that have use a variety of experimental models, including humans. In nutritional amounts, boron promotes bone health and brain function, modulates the immune or inflammatory response, and influences the response to oxidative stress. 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. Based on findings from both animal and human experiments, an intake of boron near 1.0 mg/day would be a reasonable suggestion for an adequate intake that would assure the benefits provided by boron.

Increased intakes of boron through consuming fruits, vegetables, nuts, and pulses should be recognized as a reasonable dietary recommendation.

## 1. Introduction

Boron has been shown to be essential for the completion of the life cycle (i.e., deficiency cause impaired growth, development, or maturation such that procreation is prevented) for organisms in all phylogenetic kingdoms [1]. In the animal kingdom, deprivation of boron was shown to adversely affect reproduction and embryo development in both the African clawed frog (*Xenopus laevis*) and zebra fish [2, 3]. Experiments with mammals have not shown that the life cycle can be interrupted by boron deprivation, nor has a definite biochemical function been defined for it. However, substantial evidence has been reported indicating that boron in nutritional and supra nutritional amounts has numerous diverse effects beneficially affecting the health and well-being of animals and humans. Since 2008, the focus of most reports has been on boron beneficially affecting bone growth and maintenance and the modulation of oxidative and inflammatory stress, which ultimately affect the susceptibility to and/or severity of pathological conditions such as arthritis, cardiovascular disease, osteoporosis and cancer.

## 2. Health effects

### *2.1. Bone growth and Maintenance*

The first report indicating that boron could beneficially affect bone health appeared in 1981 [4]. Boron deprivation was found to exacerbate gross bone abnormalities in chicks fed marginal amounts of vitamin D. In 1994, Hunt et al [5] reported that boron deprivation decreased chondrocyte density in the zone of proliferation of the bone growth plate in chicks. Boron deprivation was reported to decrease bone strength in pigs [6] and rats [7] in 2000 and 2004, respectively. In 2008, boron deprivation (0.7 vs. 3 mg/kg diet) in rats was reported to decrease the repair of alveolar bone (primary support structure for teeth) that is initiated immediately after tooth extraction [8]. The osteoblast surface was decreased and the quiescent bone-forming surface was increased in the alveolus. Boron deprivation also was found to decrease alveolar bone formation without tooth extraction in mice [9]. Boron deprivation decreased the osteoblast surface and increased the quiescent bone-forming surface in both the lingual and buccal sides of periodontal alveolar bone. Consistent with these findings were the findings that boric acid supplementation (3 mg/day for 11 days or 15 mg / day for 15 days) inhibited alveolar bone loss in rat periodontitis models [10,11], and 3 mg boron gavage/kg body weight/96 hours increased alveolar bone mineral density in rabbits fed a high-energy diet [12].

Since the findings above, over 20 reports have appeared indicating that boron can beneficially affect bone growth and maintenance. Cell culture studies have been prominent in these reports. They have shown that boron enhances osteogenic differentiation of human tooth germ stem cells [13] and bone marrow stromal cells [14], differentiation and osteogenic ability of differentiated bone marrow mesenchymal stem cells [15], and differentiation and gene expression of pre-osteoblastic cells and osteoblasts [16, 17].

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Mineralized tissue genetic expression and biochemical changes found in the cell culture studies include increased mRNA expression of type 1 collagen, osteopontin, bone sialoprotein, osteocalcin and RunX2 in osteoblasts treated with 1 and 10 mg/mL boron vs. controls not receiving boron [16]. The boron treatments also increased bone morphogenetic proteins 4, 6, and 7 levels. Subsequent reports also found that boron supplementation of cultured cells increased the genetic expression of osteocalcin, collagen type 1, vascular endothelial growth factor, RunX2, and bone morphogenetic protein 7 [13, 14, 17]. In addition, the boron supplementation increased bone alkaline phosphatase activity [13, 14].

Modification of bioactive glasses, which is used for bone tissue engineering and regeneration, to contain boron also indicates that this element has beneficial bioactivity in bone. This modification enhances bone formation [17-20]. Some of this beneficial activity has been attributed to increasing osteoblast gene expression of alkaline phosphatase, osteocalcin, collagen type 1, RunX2, and bone sialoprotein in osteoblasts [17, 20]. Another reported suggestion is that boron enhances angiogenesis (blood vessel formation) critical for wound repair and tissue engineering. Ionic dissolution of borosilicate bioactive glass resulting in stimulated umbilical vein endothelial cell proliferation and migration associated with phosphorylation of extracellular signal-related kinase ½, focal adhesion kinase, and p38 protein was attributed to the release of boron [21]. Boron from ionic dissolution of bioactive glass also was assessed as the factor that promoted angiogenesis in embryonic quail chorioallantoic membrane [22].

Supra nutritional or pharmacological intakes of boron also have been found to beneficially affect bone. These intakes have been found to stimulate bone formation induced by orthopedically expanded suture in rabbits [23], improve fracture healing in rats [24], and increase tibia bone density in ostrich chicks [25].

A recent supplementation study supports the contention that boron has beneficial effects on bone in humans. Six mg of boron as calcium fructoborate, a naturally occurring complex commonly found in fruits and vegetables, was incorporated into margarine and fed to 100 patients with osteoporosis for six months [26]. Bone density was improved in 66 of the patients. This finding indicates that more studies are needed to determine whether boron intake can be a factor affecting bone health in humans.

### *2.2. Modulation of inflammatory and oxidative stress*

In 1990, the first indication that boron could affect inflammatory and oxidative stress appeared [27]. In a double-blind study, 15 individuals with confirmed osteoarthritis, which is associated with chronic inflammation, were given either a supplement of six mg of boron or placebo daily for eight weeks. Five of the seven subjects consuming the boron supplement reported improved subjective measures such as less pain on movement and less swelling of their arthritic joints and less use of analgesic pain relievers. Only one of eight subjects consuming the placebo reported improvement of their arthritic condition. Similar results were described in a 2009 report describing the effect of a daily boron supplement of 6 mg/day as calcium fructoborate on subjective measures of mild, moderate, or severe osteoarthritis in 20 subjects [28]. After eight weeks of supplementation, 80% of the mild or moderate arthritic individuals reported reduced or eliminated use of pain killers. In addition, joint rigidity essentially disappeared and mobility was markedly increased. These findings, however, were weakened by the non-blinding to treatment and lack of placebo controls.

Early animal studies also indicated that boron inhibits inflammatory stress such as that found in arthritic conditions. Feeding a supplemental 2 mg boron/kg diet decreased the swelling and the onset of induced arthritis in rats fed a diet containing 0.1 mg boron/kg [29, 30]. Supplementing 5 mg boron/kg to a diet containing 2 mg boron/kg decreased the skinfold thickness response to an intradermal injection of phytohemagglutinin in pigs [31]. The boron-supplemented pigs also had increased serum concentrations of the inflammatory cytokine tumor necrosis factor-α (TNF-α) [32].

Since 2008, over 25 reports have appeared indicating that boron can modulate the response to inflammatory and oxidative stress. These reports have involved studies with animals and cells with induced oxidative stress and supplementation and epidemiological studies of individuals with elevated oxidative and inflammatory stress.

Among the cell culture studies are those showing that boric acid inhibited lipopolysaccharide (LPS)-induced TNF-α formation through a thiol-dependent mechanism in human monocytic leukemia THP-1 cells [33]; calcium fructoborate decreased interlukin-1β (IL-1β) and interlukin-6 (IL-6) release by LPS-stimulated murine macrophage RAW 264.7 cells [34]; borate inhibited micronucleus and sister chromatid exchange formations induced by aflatoxin B1 [35]; boric acid provided protection against the induction of DNA strand breaks and micronuclei by lead and cadmium toxicity [36]; and boric acid protected chromosome structure in human primary alveolar epithelial cells treated with nicotine [37] .

Among the animal studies are those showing that boric acid increased the anti-oxidant capacity of spleens in rats [38]; boric acid had anti-oxidant action that prevented damage to membranes of the cerebral cortex

of rat pups induced by alcohol treatment of dams [39]; boric acid inhibited lipid peroxidation induced by arsenic trioxide in rats [40]; and boron increased serum total anti-oxidant activity, and hepatic expression of both Cu-Zn superoxide dismutase and Mn-superoxide dismutase mRNA in in rats injected with sheep red blood cells in the footpad [41].

The cell and animal studies showing boron has anti-inflammatory and anti-oxidant activities support the findings indicating boron has similar actions in humans. In a 2011 report [42], 60 individuals with primary osteoporosis were divided into groups of 15 and supplemented with a placebo or boron at 3, 6, or 12 mg daily as calcium fructoborate for 15 days in a double-blind fashion. When compared to the placebo group, all boron-supplemented individuals grouped together exhibited improved inflammation biomarkers of C-reactive protein (CRP), fibrinogen, and erythrocyte sedimentation rate. The strength of this anti-inflammatory effect of boron was weakened by the shortness of supplementation and the lack of an indication of the boron status of the individuals, such as boron dietary intake or plasma concentration, at the start of the study. However, some of the individuals may have had a low boron status because, in another study, the mean serum boron concentration was significantly lower in 43 individuals with knee osteoarthritis than in 18 healthy controls [43]. Serum boron negatively correlated with the duration and severity of the osteoarthritis. Also, mean sedimentation rate and white blood cell count were higher in osteoarthritic individuals than controls. Rheumatoid arthritis also is characterized by chronic inflammation. In a cross-sectional study the mean serum boron concentration was significantly lower in 107 patients with rheumatoid arthritis than in 214 controls matched in age and sex [44].

Two studies have found that boron supplementation reduced CRP in individuals with serum CRP concentrations greater than 3.0 mg/L, which is considered an indicator of chronic inflammatory stress. In a randomized, double-blind, parallel clinical trial, boron supplemented at 6 mg/day as calcium fructoborate significantly decreased elevated CRP in 29 patients with stable angina pectoris, while 29 patients without supplementation showed no change at both 30 and 60 days [45]. In another double-blind, placebo-controlled clinical study, groups of 26-28 healthy individuals with mean serum concentrations greater than 3.0 mgl/L were given a placebo or supplemented with boron at either 3 or 6 mg/day as calcium fructoborate for 30 days [46]. Compared to the placebo group, both boron supplementations significantly reduced serum concentrations of CRP, IL-6, and monocyte chemoattractant protein-1.

Because inflammation and oxidative stress also has been associated with the risk for cancer, recent findings showing an association between low boron status and some cancers might be related to anti-inflammatory and antioxidant bioactivity of boron [47]. In 2004, an epidemiological study found an inverse association between dietary boron and prostate cancer [48]. Subsequently, reports have described the inhibitory effect of boron on the growth or proliferation of some types of cultured prostate cancer cells [49-51]. Boron supplementation also was found to decrease growth and mitotic figures in human prostate adenocarcinoma tumors in nude mice [52].

Boron also has been inversely associated with other forms of cancer. Cervical smears from 587 women with a mean boron intake of 1.26 mg/day found 15 cases with cytopathological indications of cervical cancer, but none was found in 472 women with a mean boron intake of 8.41 mg/day [53]. In a study of 763 women with lung cancer and 838 matched controls, boron was inversely associated with the incidence of lung cancer [54]. Boron was found to inhibit the proliferation of cultured breast cancer cells in a dose-dependent manner [55].

### *2.3. Central vervous system function*

Findings showing that nutritional intakes of boron have beneficial effects on central nervous system function are among the most supportive of the concept that boron is a beneficial bioactive trace element for humans. In the 1990s, boron supplementation after deprivation under well-controlled dietary conditions resulted in electroencephalograms indicating improved behavior activation (e.g., less drowsiness and increased mental alertness) in men and women [56, 57]. Psychomotor skills of motor speed and dexterity, and cognitive processes of attention and short term memory were also improved. Unfortunately, no further studies of these effects of boron have been reported.

Limited studies with animal models have supported the human central nervous system findings. Early studies with rats found that boron deprivation affected brain electrical activity in a manner similar to nonspecific malnutrition and heavy metal toxicity [58]. Boron-deficient zebrafish were found to develop photophobia, which apparently was caused by photoreceptor dystrophy [59]. More recently, boron-deprived rats were found to be less active than boron-supplemented rats based on variables determined in a spontaneous activity evaluation [60].

## 3. Mechanisms of action

The diverse beneficial effects reported for boron as summarized in Table 1 have made it difficult to determine the primary mechanisms of action for its bioactivity. The diverse responses are probably 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 may be indicating the possible basis for its bioactivity. Boric acid forms ester complexes with hydroxyl groups of organic compounds [61]. This preferably occurs when the hydroxyl groups are adjacent and in the *cis* orientation. This property results in the formation of complexes with several biologically important sugars, including ribose [61].

Ribose is a component of adenosine. Some of the diverse actions of boron could occur through its reaction with biomolecules containing adenosine or formed from adenosine precursors. These compounds include S-adenosylmethionine (SAM) and diadenosine phosphates that have higher affinities for boron than any other recognized boron ligand in animal tissues [62]. Diadenosine phosphates are present in all animal cells and function as signal nucleotides associated with neuronal response. S-Adenosylmethionine is one of the most frequently used enzyme substrates in the body. About 95% of SAM is used in methylation reactions, which influence the activity of DNA, RNA, proteins, phospholipids, hormones, and transmitters.

Support for the suggestion that boron beneficial bioactivity may be associated with SAM is the finding that the bacterial quorum-sensing signal molecule, auto-inducer-2 (AI-2), is a furanosyl borate ester synthesized from SAM [63]. Quorum-sensing is the cell-to-cell communication between bacteria accomplished through the exchange of extracellular signaling molecules (auto-inducers). Support also is provided by the finding that boron deprivation increased plasma homocysteine (formed from SAM) and decreased liver SAM in rats [64]. High circulating homocysteine and depleted SAM have been implicated in many of the disorders suggested to be affected by nutritional intakes of boron, including osteoporosis, arthritis, cancer, diabetes, and impaired nervous system function.

Boron also strongly binds oxidized nicotinamide adenine dinucleotide (NAD). Thus, boron could influence reactions in which oxidized NAD is involved. One role of oxidized NAD is binding to the plasma membrane receptor CD38, which is an adenosine diphosphate (ADP) ribosyl cyclase that converts oxidized NAD to cyclic ADP ribose. Cell culture studies show that boron in physiological concentrations binds to and is a reversible inhibitor of cyclic ADP ribose [65]. Cyclic ADP ribose is released intracellularly and binds to the ryanodine receptor, which results in the release of $Ca^{2+}$ from the endoplasmic reticulum and thus lowers its $Ca^{2+}$ content. Low endoplasmic reticulum $Ca^{2+}$ can induce endoplasmic stress which activates the eukaryotic initiation factor 2α (eIF2α) and increases activating transcription factors 4 (ATF4) and 6 (ATF6) [65, 66]. The increase in ATF6 induced by boron increases the expression of downstream genes binding immunoglobulin protein (BiP), calreticulin, endoplasmic reticulum degradation enhancer mannosidase (EDEM), and GR94 [51]. ATF4 and BiP are involved in osteogenesis, calreticulin is required for tumor suppressor p53 function, and Bip and EDEM prevent the aggregation of misfolded opsins that leads to retinal degeneration [51]. As indicated above, low boron status has been associated with impaired bone formation and maintenance, increased cancer risk, and retinal degeneration.

Another hypothesized mechanism through which boron is bioactive is the formation of diester borate complexes with phosphoinositides, glycoproteins, and glycolipids, which contain *cis*-hydroxyl groups, in membranes

**Table 1.** Diversity of Beneficial Bioactivity of Boron

| Beneficial action | Health impact | Supporting references |
|---|---|---|
| Anti-Inflammatory/Anti-0xidant | Osteoporosis | 26 |
| | Osteoarthritis | 27-30 |
| | Oxidant Stress Pathology | 33-41 |
| | Inflammatory Stress Pathology | 42-46 |
| | Cancer | 47-52 |
| Cell Membrane Function | Embryo development | 3 |
| | Central Nervous System Function | 59 |
| Gene Expression/Enzyme Activity | Bone growth/development | 5-20, 65-66 |
| | Angiogenesis | 21-22 |
| Hormone Facilitator | | |
| Estrogen | Bone Health | 72-75 |
| Insulin | Energy metabolism | 46, 76 |
| Progesterone | Reproduction | 2 |
| Thyroid Hormone | Energy Utilization | 2, 31, 46, 70 |
| Vitamin D | Bone growth/structure | 4, 69 |
| S-Adenosylmethionine Function | Cardiovascular disease | 62, 63 |
| | Bone Health | 62, 63 |
| Signal Transduction Modulator | Central Nervous System Function | 56-58, 60, 62 |
| | Hormone and $Ca^{2+}$ Action | 63, 68 |

[67]. These diester borate polyl complexes could act as calcium chelators and/or redox metabolism modifiers that affect membrane integrity and function. The finding that the borate transporter NaBC1, which apparently is essential for boron homeostasis in animal cells [68], conducts $Na^+$ and $OH^-$ across cell membranes in the absence of boron supports the suggestion that boron affects the transduction of regulatory ions across cell membranes. Modification of cell membrane integrity and function may partly responsible for the findings that boron can influence animal and human responses to some hormones, including vitamin D (4, 5, 69) thyroid hormones [2, 31, 70], progesterone [71], estrogen [72-75], and insulin [76].

Boron also might affect health through increasing the abundance of the quorum sensing AI-2 in the microbiome. Recently, it was found that increasing the amount of AI-2 in the gut of antibiotic-treated, mice help reinstate the populations of beneficial bacteria [77].

### *3.1. Beneficial intakes*

Both animals and humans deprived of boron exhibit beneficial responses to intakes of boron that may be achieved through dietary means or in nutritional amounts. In human depletion-repletion experiments, participants responded to a 3 mg/day boron supplement after consuming a diet supplying boron at only 0.2-0.4 mg/day [56, 57, 78]. There is a report that about 1 µg boron/g diet meets the needs of most all chicks [79]. Using an assumption that humans may consume 500 g diet per day, this animal study suggests a boron intake of at least 0.5 mg/day would be beneficial to many individuals, and this is consistent with the human studies. The human and animal findings were used to arrive at a mean population boron intake of 1.0 mg/day to meet the normative needs of adults [80]. Thus, achieving a boron intake of 1.0 mg/day should provide optimal beneficial activity in healthy adults. Higher amounts might be beneficial in individuals with pathological conditions associated with chronic inflammatory and oxidative stress.

Boron is relatively non-toxic food component. The safe upper intake level (UL) of boron in the United States and Canada has been set at 20 mg/day [81]. The World Health Organization first suggested that 13 mg/day would be a UL [80], but later increased this to 0.4 mg/kg body weight or about 28 mg/day for a 70 kg person [82]. The European Union established an UL for total boron based on body weight that results in about 10 mg/day for adults [83].

An intake of 1.0 mg/day can be easily achieved by consuming foods of plant origin. Foods rich in boron include fruits, leafy vegetables, nuts, legumes, and pulses [84, 85]. Beverages based on fruits and grains, such as wine, beer and cider are also good sources of boron.

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