Biological Effects of Boron

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1 Introduction

Boron, which bears the symbol B in the periodical table, is a semiconductive element with properties between that of a metal and a nonmetal (Kılıç et al. 2009). This micro-mineral is ingested with foods on a daily basis, and the amount taken in varies with the levels that occur in the consumed food and drink (Sabuncuoglu et al. 2006).

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This element is a chemically dynamic trace element that forms approximately 230 compounds, generally with other elements (World Health Organization 1998; Kılıç et al. 2009).

Boron exists at high concentrations in sedimentary rocks, soils, coal, and seawater (Samman et al. 1998). It is estimated that the global average concentration of boron in seawater is approximately 4.6 mg/L (Samman et al. 1998). Boron is released into the atmosphere from commercial uses, forest fires, coal combustion, and volcanoes. It reaches the ocean as a result of rock weathering, which constitutes another atmospheric source (Howe 1998). Sixty-five to eighty-five percent of boron in the atmosphere is derived from the world's oceans (Argust 1998).

Boron is a component of several manufactured goods, such as glass, detergents, ceramics, and fertilizers, and may reach the environment as a result of being released from these materials or during their production (Argust 1998). Seven to eighteen percent of environmental B derives from several major "anthropogenic" sources, viz., fertilizers, wastewater treatment plant releases, and fly ash waste released by coal-fired power plants (Howe 1998).

Boron is primarily a natural product and generally occurs in the environment as borates (Howe 1998). Borates are boron–oxygen compounds that result from the binding of boron with oxygen. When administered to animals, inorganic borates are biotransformed into boric acids and are absorbed from mucosal surfaces. More than 90% of the borate administered to humans or animals is excreted as boric acid. In both in vitro and in vivo systems, boric acid shows an affinity for *cis*-hydroxyl groups, and such affinity may account for the mechanism by which boric acid produces some of its biological effects (World Health Organization 1998; Bolaños et al. 2004).

Recent studies on the biological significance of boron to various metabolic, nutritional, hormonal, and physiological processes indicated that B may (Blevins and Lukaszewski 1998) or may not (Loomis and Durst 1992) be essential to plants, but B is essential for humans and animals (Nielsen 1997; Basoglu et al. 2000, 2002; Kabu and Civelek 2012; Hunt 2012). It is accepted that boron performs functions in mineral metabolism, in immune response, and in the endocrine system. Furthermore, boron is metabolically important for bone growth and health (Nielsen 1997; Basoglu et al. 2000, 2002; Kabu and Civelek 2012; Hunt 2012). Unfortunately, the detailed mechanism by which boron functions in animals has not yet been fully described.

Our purpose in this chapter is to summarize the current status of knowledge on how boron functions metabolically in living organisms, and produces effects on living organisms.

2 The Importance of Boron for Living Organisms

2.1 Animals

It is now known that boron is a necessary dietary component for humans and animals (Hunt 1994; Nielsen 1997; Kabu and Civelek 2012). Boron meets most criteria as an essential nutrient (Hunt 1998). It has a low atomic weight and binds to organic

compounds in ways that influence biological function (Hunt 1998). At the levels boron normally exists in organisms, it is generally nontoxic, and animals tend to have a natural ability to maintain homeostatic control of boron levels in their bodies (Hunt 1998). Notwithstanding, even rather low levels of dietary boron intake in some animal species have been associated with developmental abnormalities (Hunt 1998).

Several studies have been performed to investigate the effects of boron intake on animals. Researchers believe that sodium borate ($Na_2B_4O_7$) protects against developing a fatty liver (Basoglu et al. 2002; Bobe et al. 2004). Because treating the fatty-liver condition in cows is costly and difficult to perform, preventing the disease is a much better approach than having to treat for it after it occurs (Bobe et al. 2004). In one study on cows, significant decreases were observed in serum triglyceride (TG) and very low density lipoprotein (VLDL) levels of animals treated orally with sodium borate (Basoglu et al. 2002). Kabu and Civelek (2012) studied the effects of sodium borate ($Na_2B_4O_7 \cdot 5H_2O$) orally administrated to 12 pregnant cattle at 30 g/day over a 28-day period that included 2-week prepartum and 2-week postpartum exposures. In this study, the effects of sodium borate on selected hormone levels and serum metabolites were investigated in both treated and control animals. Blood samples were obtained weekly. Results were that no differences vs. controls were recorded in blood for concentration of total protein (TP), albumin (ALB), blood urea nitrogen (BUN), alanine aminotransferase (ALT), total bilirubin (TBil), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT). Glucose levels were higher during the prepartum period, and the postpartum glucagon and β-hydroxybutyric acid (BHBA) serum levels were higher in the control group (Kabu and Civelek 2012). At the end of sodium borate administration, concentrations of total cholesterol (TChol), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low density lipoprotein (VLDL), glucose, insulin, and nonesterified fatty acids (NEFA) in blood were decreased (Kabu and Civelek 2012). In summary, administering sodium borate may improve the metabolic situation during the periparturient period (Kabu and Civelek 2012), and the use of sodium borate in cattle during the early lactation period reduces the incidence of fatty liver (Basoglu et al. 2002).

There is evidence that, in some manner that is not yet known, boron balances harmful liver effects by altering oxidative stress parameters and acts to return the liver to its normal level of function (Pawa and Ali 2006). In another study that addressed the effects of B on fatty liver, New Zealand Rabbits were investigated (Basoglu et al. 2010, 2011). The rabbits were administered boron orally at doses of 10, 30, and 50 mg/kg of body weight (Boraks deka hidrat $Na_2B_4O_7 \cdot 10H_2O$) at 96-h intervals (Basoglu et al. 2010). These exposure levels did not affect hematological parameters of the rabbits (Basoglu et al. 2010). Basoglu et al. (2010) suggested that boron has positive effects on hepatic steatosis and visceral fat by reducing oxidative stress and by affecting the lipid profile, although the dose of 50 mg/kg had no stabilizing effects (Basoglu et al. 2010). The author concluded that boron apparently prevents fatty liver by acting on mitochondria. There was evidence in this study that boron affects the Krebs cycle, the glucose–alanine cycle, and methionine metabolism, all of which reduce oxidative stress and positively affect the lipid profile (Basoglu et al. 2011).

Basoglu et al. (2000) fed dogs a daily diet of 4 g/day of borax ($Na_2B_4O_7 \cdot 10H_2O$). That administration level was effective in keeping plasma lipid levels of the dogs low. One week after oral administration of borax, a decrease of glucose, insulin, and apolipoprotein B-100 (Apo-B100) levels was detected in treated dogs vs. controls. A decrease in VLDL and TG levels was also seen after the second week of exposure (Basoglu et al. 2000). These findings supported the conclusion that borax exposure reduced blood lipid levels (Basoglu et al. 2000).

In other studies, exposure of chicks to boron alone increased plasma glucose concentrations, particularly when a vitamin D deficiency existed (Simon and Rosselin 1978; Hunt 1989; Hunt and Herbel 1993). However, in chicks, supplemental dietary boron improved the vitamin D_3 deficiency-induced elevations that existed in plasma glucose concentrations (Hunt et al. 1994). Moreover, in vitamin D-deficient chicks, abnormally elevated plasma concentrations of pyruvate, BHBA, and triglycerides existed that are typical of vitamin D deficiency; the addition of dietary boron mitigated these effects (Hunt et al. 1994). In rats, a deficiency of boron produced vitamin D deficiency, which similarly decreased plasma TG concentrations and increased plasma pyruvate concentrations (Hunt and Herbel 1991–1992). Boron had no such effect when the diet contained sufficient amounts of vitamin D (2,500 IU/kg) (Hunt and Nielsen 1981; Hunt and Herbel 1993; Hunt 1989, 1994). How boron deficiency affects energy substrate metabolism in animal models is unknown, and this is particularly true when there are suboptimal amounts of food intake (Bakken and Hunt 2003). Boron deficiency has also caused hyperinsulinemia in rats that were deprived of vitamin D (Hunt and Herbel 1991–1992). It is claimed that an absence of boron increased the amount of insulin required to maintain plasma glucose concentrations, when either vitamin D or magnesium nutriture was perturbed in chicks and rats (Bakken and Hunt 2003).

Hunt et al. (1983) suggested that boron affects vitamin D_3 metabolism or vitamin D_3's effect on growth. DeLuca and Schnoes (1983) manipulated the dietary concentrations of magnesium or calcium to examine the interaction that occurs between dietary vitamin D_3 intake and boron levels. Magnesium deficiency was chosen as a stressor of vitamin D_3 metabolism, because it is a cofactor for the hydroxylation of 25-hydroxycholecalciferol (OH) vitamin D_3 (DeLuca and Schnoes 1983). In another study, boron added to the diet of chickens at a level of 3 mg/kg induced magnesium deficiency (300 mg/kg) and fostered bird growth (Hunt and Nielsen 1981).

The basal model daily diet for chickens contains 10% clover (4.2 mg boron/kg), lab rat daily diets contain 12–13.7 mg boron/kg (Hunt et al. 1988), and human vegetarians consume daily diets containing at least 2 mg boron/kg (Hunt et al. 1991). Yet, the amount of boron in the basal diets of research animals, in studies carried out before 1950, generally had either insufficient or excessive boron levels (100–2,200 mg/kg) (Hunt 1998). If boron is added as a supplement to diets of severely potassium-deficient rats that contain levels of 100–1,000 mg boron/kg, a positive effect on survival and maintenance of body fat and elevated liver glycogen resulted (Hunt 1994).

2.2 Humans

The major source of boron entry into the human body is via consumed food. High boron levels exist in fruits, vegetables, pulses, legumes, and nuts, whereas other foods have lower levels. Humans may also acquire boron by consuming certain beverages, or by absorbing B by respiration or through the skin (Nielsen 1997). Boron, once in the body, may be rapidly excreted via urine and does not accumulate in tissues. Boron exists in body tissues and fluids as boric acid ($B(OH)_3$) (Sutherland et al. 1998). In healthy people, total boron blood concentrations are in the range of 15.3–79.5 ng/g wet wt (Clark et al. 1987) and exist as 98.4% boric acid and 1.6% as borate anion ($B(OH)_4$) (Sutherland et al. 1998; Nielsen 1997). Boron content of the various bodily organs varies; values for the heart, liver, lung, kidney, and brain gave levels of 28, 2.31, 0.6, 0.6, 0.06 ppm boron, respectively (Hamilton et al. 1972; Indraprasit et al. 1974; Massie et al. 1990; Nielsen 1997). This suggests that any function carried out by boron differs from organ to organ (Newnham 1991).

Boron can affect the function or composition of the brain, and the skeletal and immune systems (Nielsen 1997). Dietary intake of a daily amount of boron (viz., 3 mg) for more than 7 weeks may prevent osteoporosis in postmenopausal women. After boron was consumed as a supplement, the urinary excretion of the essential elements, calcium and magnesium, decreased by 40% and 33%, respectively (Nielsen et al. 1987). In another study (Nielsen 1990), dietary boron produced effects similar to estrogen supplementation in women who suffer from postmenopausal osteoporosis. Boron intake also increased amounts of ionized calcium in the blood serum, decreased serum calcitonin concentrations, and increased serum levels of 1,25-dihydroxycholecalciferol. Dietary boron helps maintain serum calcitonin level, which assists postmenopausal women who suffer from osteoporosis (Nielsen 1990). Penland (1998) performed a study in which inadequate dietary boron intake lowered performance on cognitive and motor tests.

In human males, an orally administered daily dose of 10 mg/day of boron as sodium tetraborate for seven days produced a significant decrease in sex hormone globulin binding (SHGB), high sensitive CRP (hsCRP), and TNF-α levels. Moreover, the mean free testosterone levels in blood plasma increased, and plasma estradiol was significantly decreased (Naghii et al. 2011).

The average amount of boron taken in by humans on a daily basis varies by gender and age. Infants aged 0–6 months, males aged 51–70 years, and lactating females consumed 0.75 ± 0.14 mg/day, 1.34 ± 0.02 mg/day, and 1.39 ± 0.16 mg/day, respectively (Hunt 2012). It was determined that the average daily boron intake in adult males was 1.21 mg/day or 1.52 mg/day (Iyengar et al. 1990; Anderson et al. 1994).

2.3 Plants

Boron is an essential micronutrition for higher plants (Blevins and Lukaszewski 1998). Boron is important in sugar transport, cell wall synthesis and lignification,

cell wall structure, carbohydrate metabolism, RNA metabolism, respiration, indole acetic acid metabolism, phenol metabolism, and membrane transport (Blevins and Lukaszewski 1994; Camacho-Cristóbal et al. 2008). The significance of boron to cell wall structure and membrane function is particularly important (Blevins and Lukaszewski 1994; Camacho-CristÓbal et al. 2008).

Fruits, vegetables, and hazelnuts are known to be primary sources of boron (Hunt et al. 1991). Among vegetables, leafy greens have the highest boron levels, especially when they are grown without chemical fertilizers (Newnham 1977). Vegetables, fruits, legumes, and tubers have much higher amounts of boron than do the grasses (e.g., wheat, rice, and corn retain <0.2 mg/kg) (Nielsen 1988; Vanderpool and Johnson 1992). Dried legumes, fruits, avocados, and nuts contain from 1.0 mg to 4.5 mg boron/100 g (Naghii 1999). Fresh fruits, vegetables, honey, and bee pollen contain from 0.1 to 0.6 mg boron/100 g, whereas foods from animal sources have boron at levels between 0.01 and 0.06 mg/100 g (Newnham 1977; Naghii 1999).

The position of the hydroxyl group on the boron atom makes formation of complexes with substrates and other reactants easier (Dugger 1983). Boron may have a significant role in adjusting or regulating certain metabolic functions in plants (Hunt 1994). From studies performed on higher plants (Lovatt and Dugger 1984; Goldbach 1997) and in animals in which human nutrition was evaluated, the position of the hydroxyl group on the boron appeared to be critical (Nielsen et al. 1988; Hunt 1989; Hegsted et al. 1991; Hunt and Herbel 1991–1992, 1993; Bai and Hunt 1996; Eckhert 1998; Fort et al. 1999; Armstrong et al. 2000). Boron may affect metabolic pathways by binding apoplastic proteins to *cis*-hydroxyl groups of cell walls and membranes, and by interfering with manganese-dependent enzymatic reactions. Recently, the formation of borate esters with hydroxyl groups of cell wall carbohydrates and/or glycoproteins has been proposed as a mechanism for cross-linking cell wall polymers (Loomis and Durst 1992). Borate bridging could explain many of the characteristics observed in boron-deficient plants (Blevins and Lukaszewski 1998).

Boron deficiency in plants causes carbohydrate accumulation in chloroplasts, accelerates the activity of the pentose phosphate cycle, and may slow the Krebs cycle (Goldbach 1997; Lovatt and Dugger 1984). The amount of boron available in soils varies with the fertilizers used, and with soil type, temperature, and pH (Newnham 1977). The application of potash fertilizers and superphosphate fertilizers inhibits boron absorption (Newnham 1977). Warm, moist soil renders boron more bioavailable because of increased microfloral activity (Newnham 1977).

2.4 Bacteria and Fungi

Borates produce effects on a variety of bacteria and fungi (Woods 1994; Hunt 2003; Kartal et al. 2004; Rolshausen and Gubler 2005; Baker et al. 2009; Tamay-Cach et al. 2012; Hunt 2012). Hunt (2003) suggests that boron is an essential trace element for at least some organisms in each of the following taxa: Eubacteria, Stramenopila (brown algae and diatoms), Viridiplantae (green algae and familiar green plants), Fungi, and Animalia.

Ahmed and Fujiwara (2010) reported that B is toxic to living cells at levels above a certain threshold. They isolated several B-tolerant bacterial strains from soil samples and studied their possible mechanisms of tolerance to B. They sequenced the gene16S rRNA and performed comparative phylogenetic analysis, which showed that the isolates they studied belonged to the following six genera: *Arthrobacter*, *Rhodococcus*, *Lysinibacillus*, *Algoriphagus*, *Gracilibacillus*, and *Bacillus*. These isolates exhibited tolerance levels to B of 80, 100, 150, 300, 450, and 450 mmol/L, respectively, while maintaining a significantly lower intracellular B concentration than in the medium. Statistical analysis demonstrated a negative correlation between the protoplasmic B concentration and the degree of tolerance to a high external B concentration. The kinetic assays suggest that the high B efflux and (or) exclusion are the mechanisms by which the high external B concentration in the isolated bacteria are tolerated.

Boron, in several forms, is active against several wood decay fungi (Smith 1970; Schultz et al. 1992; Cookson and Pham 1995; Kartal et al. 2004), and therefore it is used in the timber industry to protect wood from termites and fungi (Kartal et al. 2004) and in forestry to prevent infection of conifers by *Heterobasidion annosum* (Fr.) Bref. (=*Fomes annosus* (Fr.) Karst.) (Smith 1970; Schultz et al. 1992).

Eutypa dieback is a perennial canker disease of grapevines and is caused by *Eutypa lata.* This fungus produces ascospores that infect grapevines through pruning wounds during the dormant season. Fungicide applications applied during the dormant period are known to control plant fungal diseases (Irelan et al. 1999). Rolshausen and Gubler (2005) performed a field trial to show the efficacy of boric acid treatment to control infections in pruning wounds of *Eutypa lata* in a field trial. Results were that if applied at 17.5% a.i. of boron, boric acid will control this disease. The EC_{50} values for inhibiting mycelial growth and ascospore germination were 125 and 475 μg for boric acid per ml (22 and 83 μg a.i./mL), respectively. Rolshausen and Gubler (2005) also tested two 5% boric acid treatments for the control of this canker disease in different formulations: The first (a paste) was called biopaste (8.75 mg a.i./mL) and the second treatment was called bioshield, formulated as a spore suspension of *Cladosporium herbarum*. Compared to a water control both products significantly reduced the disease incidence, both in in vitro trials and in field trials. Boron did not accumulate in leaves and shoots. But, bud failure at the first node below the treated wound occurred in B-treated plants at a higher rate than that existed in untreated vines.

3 The Effect of Boron on Enzymes and Minerals

3.1 Enzymes

Boron affects the activities of at least 26 different enzymes, most of which are necessary for energy substrate metabolism (Hunt 1998). Dugger (1983) reported in an in vitro study that boron interacted with many enzymes. Boron competitively

inhibited at least two classes of enzymes, one of which was oxidoreductase, an enzyme related to pyridine and flavin nucleotides. Borate also inhibited nicotinamide adenine dinucleotide (NAD) (Roush and Norris 1950; Strittmatter 1964; Deitrich 1967; Deal 1969). Moreover, it is known that the hydroxyl groups of NAD forms complexes with the borate compound (Johnson and Smith 1976). Boron having adjacent hydroxyl groups (transferases) has a tendency to form complexes with organic molecules. It may have an interaction with important biological substances, containing polysaccharides, pyridoxine, riboflavin, dehydroascorbic acid, and the pyridine nucleotides. (Samman et al. 1998; Deviran and Volpe 2003) It binds strongly to furanoid *cis*-diols, which include erythritan, ribose, and apiose; apiose is present throughout the cell walls of vascularplants (Loomis and Durst 1992; Hunt 2012).

Nicotinamide adenine dinucleotide (NAD+) and nicotinamide adenine dinucleotide phosphate (NADP) contain ribose components that are active in energy metabolism; binding to them affects certain metabolic pathway processes (Hunt 2012). Hunt (2012) reported that NAD+ is an essential cofactor for five sub-subclasses of oxidoreductase enzymes and has a strong relevance for boron. The di-adenosine-phosphates (Ap_nA) are structurally similar to NAD+. Compared to NAD+, boron binding by Ap_4A, Ap_5A, and Ap6A is greatly enhanced; however, the binding is still less than that to *S*-adenosylmethionine (SAM).The adenine moieties of Ap_nA are driven together by hydrophobic forces and clump interfacially. Stacking of the terminal adenine moieties brings their adjacent ribose moieties into close proximity, which is the phenomenon that apparently potentiates the cooperative boron binding between opposing riboses (Hunt 2012). Boron's distinctive chemistry allows it to react with many other metabolites and enzymes and thus may be capable of modifying mineral and energy metabolism in humans and animals (Deviran and Volpe 2003).

Boron may have a major role in controlling certain pathways that use serine proteases (hydrolases) or oxidoreductases (Hunt 1998, 2012). These enzymes require pyridine or flavin nucleotides (NAD+, NADP, or FAD), and by forming transition state analogs or competing for NAD or FAD, boron reversibly inhibits their activity (Hunt 1998, 2012). Serine proteases, such as thrombin, functions in regulating blood and coagulation systems. Other enzymes such as phosphoglucomutase, λ-glutamyl transpeptidase (GGT), and glyceraldehyde- 3-phosphate dehydrogenase (GPD) are also inhibited by boron (Hunt 1998; Deviran and Volpe 2003).

Boron is known to inhibit certain other enzymes (viz., aldehyde dehydrogenase, xanthine oxidase) that exist in energy metabolic pathways (Hunt 1994, 2012). Hall et al. (1989) reported that when B was orally administrated (8 mg/kg/day) to rats, daily for 14 days, LDL cholesterol and TG levels decreased. LDL bonding and LDL entrance into liver cells were also decreased, whereas fibroblasts and aorta cells showed increased HDL bonding and accumulation in liver cells. These effects were claimed to be beneficial for atherosclerosis, because they may remove cholesterol from tissues and decrease lipid accumulation (Deviran and Volpe 2003). Naghii and Samman (1997a, b) stated that boric acid intake decreased total cholesterol, HDL_3, TG, and total HDL, when given to rats for 2 weeks at a dose of 2 mg/day. However,

Green and Ferrando (1994) did not observe differences in plasma lipid concentrations, oxidation rates, LDL, or HDL fraction dispersions after 4 weeks of boric acid exposure in humans.

Ince et al. (2010) reported that boron administered to rats in the diet increased blood glutathione (GSH) concentrations and plasma vitamin C levels. In the same study, boron added to the diet at doses of 100 mg/kg increased antioxidant defense mechanisms and vitamin status of the group; neither differences between oxidant and antioxidant balance nor changes in biochemical parameters, other than serum vitamin A and liver GSH concentrations, were detected.

Another study was performed on 36 Angus and Angus-Simmental cattle that were divided into three groups. A control group received no supplementary B in their diet, a second group was fed a diet containing a 5 mg/kg supplement of B, and the third group was fed a 15 mg/kg supplement of B for 47 days to determine the effect on disease resistance to bovine herpesvirus type-1 (BHV-1). The cattle were inoculated with BHV-1 intranasally on the 34th day. On the second day following inoculation, rectal temperatures of the cattle and plasma tumor necrosis factor-α concentrations had increased ($P<0.05$). On the fourth day after inoculation, the plasma acute phase proteins had multiplied ($P<0.01$), and plasma interferon-γ levels were beginning to decline ($P<0.05$). Plasma B concentrations had increased slightly after the addition of B ($P<0.001$), whereas the dietary levels of B fed showed no significant effect on BHV-1 symptoms, and had little influence on plasma acute phase proteins and cytokines (Fry et al. 2010).

3.2 Minerals

Boron has a regulatory role in the metabolism of several minerals such as phosphorous, magnesium, calcium, and molybdenum (Wilson and Ruszler 1996). Hunt et al. (1983) showed that chicken growth was enhanced when they were exposed to boron–calcium and boron–magnesium and suggested that the relationship between magnesium and boron was stronger than that between calcium or phosphorus and boron. A relationship appeared when the boron: magnesium molar ratio was quite low in both plasma and in the consumed diet, although a direct effect of boron on magnesium metabolism was not thought to have occurred. Apparently, boron indirectly influences magnesium metabolism, and ultimately, calcium and phosphorus metabolism by influencing an enzyme or the hormone system (Hunt et al. 1983).

The regulatory role that B plays with minerals affects bone health and is particularly interesting, because it affects the relationship B has with magnesium, vitamin D, phosphorus, and calcium (Deviran and Volpe 2003; Nielsen 1990). A deficiency of boron upsets the intrinsic plasma concentration balance between calcium, magnesium, and phosphorus (Hegsted et al. 1991). Hunt and Nielsen (1986) studied magnesium-deficient chicks and found that supplemental boron decreased the incidence of abnormalities caused by insufficient magnesium intake. Subsequent boron

supplementation enhanced growth and increased plasma calcium and magnesium concentrations, and also inhibited the calcification of cartilage (Hunt 1989).

The effect that vitamin D_3 has on glycolysis may be related to calcium levels, because calcium is the main inhibitor of phosphofructokinases (limiting enzymes in glycolytic paths) (Auffermann et al. 1990). In the cartilage of rachitic rats, the glycolysis rate more than doubles, commensurate with increased activities of the phosphofructokinases, aldolase, pyruvate kinase, and lactate dehydrogenase (Meyer and Kunin 1969). Similarly, in chronic kidney failure, glucose tolerance and hyperlipoproteinemia occur, and after synthetic vitamin D_3 treatment starts, fasting blood glucose and TG levels decrease and glucose tolerance is reduced (Lind et al. 1988). Researchers have also indicted that vitamin D_3 is essential for insulin secretion (Norman et al. 1980; Gedik and Akalin 1986). A dietary vitamin D_3 deficiency reduces hepatic glycogen in rats (Davis et al. 1989). Unlike the hypothesis that is worded "lipid–carbohydrate is not transformed in the livers of mammals", glycogen content was claimed to have increased 35% after the incubation of rat liver sections to which vitamin D_3 with palmitate was added (Davis et al. 1989). Hunt et al. (1994) reported that boron modulated hepatic glycolysis when a vitamin D3 deficiency existed; moreover, when boron was added to the diet (2.25 vs. 0.16 mg/kg) it reduced effects on glycolytic metabolites such as fructose-1,6-diphosphate P_2, glycerate-2P, and $(OH)_2$-acetone P in freeze-clamped chick liver (Hunt 1989). Supplemental boron in the diet reduced the plasma pyruvate concentrations in vitamin D_3-deprived rats (Hunt et al. 1994). These data suggest that boron limits the activity of some enzymes and stabilizes reactive compounds by regulating energy substrate utilization (Hunt et al. 1994).

4 Boron Toxicity

Micronutrient elements may be toxic at some dose, duration of exposure time, and application method (Blevins and Lukaszewski 1994). The toxicity of borate compounds have been extensively studied in both laboratory and other animals. Boric acid and borax were the forms of boron most commonly administered to animals in such testing. Boric acid and borax have performed toxicologically similarly in the species to which they have been administered (World Health Organization 1998). In boron exposure studies, whether borax or boric acid was tested, data are expressed as boron equivalents to enable data comparisons (USDA Forest Service 2006). At a physiologic pH, borate salts are converted almost entirely to nonionized boric acid; hence, boric acid and borate salts have similar toxicologic features (USDA Forest Service 2006). Following oral administration, inorganic borates are well absorbed (about 90% of the administered dose) by animals (USDA Forest Service 2006).

Animal experiments revealed that toxicity results from dietary boron intake that exceeds about 100 $\mu g\ g^{-1}$. Testicular cell damage and atrophy may appear when dietary boron levels in mice exceed 4,000 mg boric acid kg^{-1}. Similar effects were shown for rats after oral administration (Nielsen 1997; EPA 2008). It was reported

that 17.5 mg B/kg per day (blood boron level of ~2,020 ng/g) affected fertility, and 9.6 mg B/kg per day (blood boron level of ~1,270 ng/g) affected the normal development of exposed rats (Price et al. 1997; Scialli et al. 2010).

In humans, acute toxicity symptoms of excessive boron exposure are nausea, vomiting, diarrhea, and lethargy (Linden et al. 1986; Nielsen 1997). Oral intake by two infants from dipping pacifiers into a preparation of borax and honey resulted in scanty hair, anemia, seizures, and patchy dry erythema, over a period of several weeks (Gordon et al. 1973; Nielsen 1997). Signs of chronic boron toxicity are poor appetite, nausea, weight loss, and decreased sexual activity, seminal volume, sperm count, and motility (Nielsen 1997; USDA Forest Service 2006). However, Duydu et al. (2012) pointed out that mean blood boron levels of boric acid workers were 223.89 ng/g, and this level was ~9 times lower than levels that produced reproductive effects in exposed rats; these levels were also ~6 times lower than levels that produced developmental effects in rats. At the levels recorded for exposed workers, no harmful effect on the reproductive system was observed. In addition, urine analyses indicated that the boron exposure of boron mine workers was 6.5 mg/day, and these levels produced no negative effects on worker semen profiles (Korkmaz et al. 2011). Workers who were exposed to the highest boron levels (i.e., 125 mg B/day) showed no significant effects on semen characteristics (Scialli et al. 2010). In conclusion, evidence suggests that the daily exposure experienced by humans to boric acid or sodium borates is unlikely to produce reproductive toxicity (Duydu et al. 2012).

An acute oral dose of borax produced an LD_{50} of 4.50 g/kg in rats and boric acid an LD_{50} of 3.45 g/kg by gavage; after dosing, rats displayed depression, ataxia, convulsions, and death (Weir and Fisher 1972). Sabuncuoglu et al. (2006) reported that a subacute dose of 400 mg/kg/day administered orally to rats produced histopathological changes in kidney tissue. A single oral dose of borax administered to dogs by capsule (at levels of 1.54–6.51 g borax/kg or 0.174–0.736 g B/kg) or boric acid administered by capsule (1.0–3.98 g boric acid/kg or 0.175–0.697 g B/kg) caused no dog deaths (Weir and Fisher 1972). The acute oral lethal dose of boric acid in 1-day-old chickens was found to be 2.95 ± 0.35 g/kg. One-day-old broiler chicks were housed in floor pens, in which the litter had been treated with 0, 0.9, 3.6, or 7.2 kg of boric acid per 9.9 m^2 of floor space. No B residue level elevation was seen in brain, kidney, liver, or white muscles of the chicks. *Ad libitum* feeding of boric acid at 500 ppm or 1,250 ppm to chicks did not alter boron levels in tissue. However, doses of 2,500 ppm or 5,000 ppm boric acid to the chicks raised residue tissue levels. Hence, it was realized that broilers grown on boric acid-treated litter do not consume enough boric acid to elevate boron levels above the norm in their tissues (viz., brain, kidney, liver, and white muscle) (Sander et al. 1991).

Restuccio et al. (1992) reported that an acute oral dose of boron in a human produced toxicity and death. A 45-year-old man drank two cups of boric acid crystals that were dissolved in water with the aim to commit suicide; the man died on the third day after consuming the boron crystals (Restuccio et al. 1992). The symptoms noted soon after consuming this dose ware nausea, vomiting, greenish diarrhea, and dehydration (Restuccio et al. 1992). Hypotension, metabolic acidosis, oliguric renal

failure, a generalized erythematous rash, and several superficial skin abrasions presented within 2 days of the exposure (Restuccio et al. 1992). The condition of the poisoned man failed to improve despite injecting intravenous fluids and vasopressors. Atrial fibrillation with a rapid ventricular response was produced and sinus rhythm could not be restored (Restuccio et al. 1992). This rhythm deteriorated to electromechanical dissociation, and the patient died 17 h after hospital admission (Restuccio et al. 1992). The urine and whole blood boric acid concentrations, approximately 52 h after ingestion, were 160 and 42 mg/dL, respectively (Restuccio et al. 1992). These results are equivalent to urine and blood boron concentrations of 28 and 7 mg/dL, respectively. The postmortem urine boron concentration was 29.4 mg/dL (Restuccio et al. 1992).

The subchronic oral administration of 1 g/kg borax and boric acid for 1–3 weeks rats produced a decrease in body weight, DNA synthesis inhibition, and clinical toxicity signs after 3 weeks (Dani et al. 1971). A 90-day test in dogs fed dietary borax at concentrations of 0%, 0.0154%, 0.154%, and 1.54% showed no treatment-related effect for any blood or urine value in males. In female dogs, hematocrit and hemoglobin decreased in the 1.54% treatment group; similarly, in the male 1.54% treatment group, testicular weights were decreased, testicular atrophy occurred, and alterations were detected in the seminiferous tubules (Paynter 1963).

A chronic oral study with borax and boric acid in rats was performed at dietary concentrations of 117, 350, and 1,170 ppm boron equivalents. Results were that no harmful effects were produced at the lower intake levels, but at the high dose level (1,170 ppm) clinical signs of toxicity occurred that included coarse hair, scaly tails, hunched posture, swelling and desquamation of the pads of paws, shrunken scrotum in males, testicular atrophy, decreased testes weight, atrophied seminiferous epithelium and decreased tubular size, as well as inflamed eyes with a bloody discharge, and a decrease in packed cell volume and hemoglobin of blood (Weir and Fisher 1972). No evidence of carcinogenesis was observed in any treatment group (Weir and Fisher 1972). Dogs fed with 1,170–2,000 ppm boron for 2 years showed stunted growth, less productive food use, skin rashes, and gonadal deterioration (Weir and Fisher 1972).

The dermal effects of boron application were investigated on ten New Zealand Rabbits by applying borax (sodium tetraborate decahydrate) as a single dose to clipped skin at 2.0 g/kg ($LD_{50} > 2.0$ g/kg) and then occluding the applied material for 2 h (Reagan 1985a). The symptoms observed on the treated animals included anorexia, decreased activity, diarrhea, soft stools, and nasal discharge (Reagan 1985a). The borax (sodium tetraborate decahydrate) application on shaved skin at 0.5 g/kg caused no skin irritation (Reagan 1985b).

Borax (sodium tetraborate decahydrate), at a dose of 0.1 g, was instilled into the eyes of six New Zealand Rabbits, caused severe irritation to the iris, and produced corneal opacity and conjunctival redness, chemosis, and discharge (Reagan 1985c). In another study, a 4 h daily inhalation of 2.0 mg/L borax (sodium tetraborate decahydrate) over 14 days in rats caused no mortality (Wnorowski 1994).

Researchers explored if borax could serve as an antidote, and, indeed, it was found to be a beneficial antagonist for aluminum toxicity (Turkez et al. 2012).

The borax (3.25 and 13 mg/kg bwt) clearly protected exposed rats against aluminum ($AlCl_3$; 5 mg/kg bwt)-induced toxicity (Turkez et al. 2012).In particular, borax blocked the increase of micronucleated hepatocytes and significantly modulated the genotoxic effects caused by $AlCl_3$ (Turkez et al. 2012).

Boron is toxic to particular processes in vascular plants. Some of the effects noted in plants included the following: altered plant metabolism, lowered cell division in roots, reduced leaf chlorophyll content and photosynthetic ratio, and reduced lignin and suberin levels, among others (Nable et al. 1997; Reid 2007). Therefore, decreased shoot and root growth is typical of plants exposed to high B levels (Nable et al. 1990). The distribution of B in leaves follows a particular pattern that extends from leaf base to tip in some plants, and this leads to particular toxicity symptoms on older leaves, which may show tip chlorosis or necrosis, or both (Marschner 1995; Roessner et al. 2006; Camacho-Cristóbal et al. 2008). Considering the chemical characteristics of B, it has been proposed that B-induced plant toxicity derives from three main causes: (a) changes to cell wall structure; (b) metabolic disorder from binding to ribose moieties in certain molecules (viz., adenosine triphosphate (ATP), nicotinamide adenine dinucleotide (reduced form) (NADH), or nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH)); and/or (c) disrupting cell division and development by binding to ribose, either the free sugar or ribose within RNA (Reid et al. 2004). Reid et al. (2004) reported that none of these proposed mechanisms have been confirmed, and further, there is no proof to support another hypothesis that leaf toxicity results from osmotic stress induced by B accumulation.

Konuk et al. (2007) investigated the effect of boron on the mitotic index of *Allium cepa* root meristematic cells. In this study, the rate of growth inhibition was first determined, and then different concentrations of boron were tested to determine effects on onion tuber roots. Distilled water was used as the control. Because the *Allium cepa* cell cycle is 24 h, B was applied at 12, 24, and 48 h. For each dose, the mitotic index and mitotic phase frequencies were calculated separately. Most abnormalities were observed to occur at c-metaphase, prometaphase, and disturbed anaphase–telophases. In addition, effects were observed on the anaphase bridge, on polyploidy, and on late chromosome particles.

5 Conclusions

Boron is thought to be an essential element for animals, people, and plants. Although several studies have been performed to determine the effects of boron on fertility and general health of animals, and human data are also available, the overall picture of how safe boron may be is still incomplete. In particular, we conclude that:

1. Boron does produce effects on human and animal bone development, mineralization, Ca, P, and Mg metabolism, energy metabolism, and activates certain enzymes. Intake of boron minerals can be effective for optimizing the treatment

of bone structure disorders, can reduce cholesterol, can improve lipid metabolic profiles, and can reduce triglyceride levels in humans and animals. In addition, sub-toxic doses of boron may be beneficial for preventing and treating type 2 diabetes and alcohol-induced fatty liver.
2. Humans and animals who reside near areas where boron is mined are exposed to this element. Therefore, research is needed both to determine what optimum levels of boron intake should be for animals and humans, and what exposure limits, if any, are needed for boron in mining regions.
3. In periparturient dairy cattle, boron intake may be particularly important for preventing or treating fatty liver, hypocalcemia (milk fever), and hypomagnesemia.
4. Boron may affect the yield and growth performance of fruits, vegetables, nuts, and grains. Although waterless borax and borax pentahydrate are used as fertilizers, their effects on plants are unclear. In addition, the effects of boron on humans and animals who consume plants or plant products to which B fertilizer was applied are unknown.
5. The effects on soil, water, or wildlife of the boron used in agriculture as both pesticide and fertilizer are unknown.

Additional research is needed to address the gaps in knowledge that were indicated above. In addition, research is needed to determine what dose of boron or boron compounds are optimal in animal rations. Finally, future research should be undertaken to enhance the understanding of how boron affects metabolic systems, and to explain how boron functions mechanistically.

6 Summary

Boron is a mineral used in human and animal health, in agriculture as a fertilizer and pesticide, and in the manufacturing of several commodities (e.g., glass, ceramics, automotive components, paint, etc.). Humans and animals consume boron daily via dietary intake. However, what the daily intake level is remains unclear. Recently, researchers have concluded that boron intake is essential for plants, animals, and humans, although insights as to what this element's biological effects are is still limited.

Although several studies on the effects of boron and how it functions have been performed over the last decade, more information is needed to clarify both its effects and how it produces its action. It is clear that boron exposure affects many enzymes and enzyme systems; some of the symptoms observed in animals from exposure to boron are explained by enzyme effects. Boron is known to produce effects on fat and lipid metabolism, on minerals and mineral metabolism, and on vitamin D. In addition, boron affects bone development. In addition, the effects of several different forms of boron on poultry and laboratory animals have been determined.

Although much of the information on boron that has already been collected is useful, much more is needed. Prospectively, the result of current research suggests that boron may be useful in the future for preventing obesity, fatty liver, and diabetes, or may be used to prevent or treat bone health problems in both humans and domestic animals.

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