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Chapter

Boron and Boron-Containing Compounds Toxicity

Çiğdem Sevim and Mehtap Kara

Abstract

Boron is an important element found in limited resources on earth, especially in Turkey, and is essential for living organisms. Boron plays key roles in human and animal systems. While boron shows its important effects as an essential element at low concentrations in the organism, it causes different toxic effects to occur at high concentrations. There are different studies on boron and boron-containing compounds effects on organisms, toxic effects mechanisms need to be detailed. Boron and its compounds can cause toxic effects in oral, dermal, and inhalation exposure and even deadly effects at very high concentrations. The use of disinfectant and cleaning products containing boron as sprays, fertilizers, etc., during the Covid-19 pandemic also increases the interest in this issue. Boron exposure could cause lung irritation, dermal irritation, genotoxicity in male reproductive system, teratogenicity in concentration-dependent manner. In vitro studies have tried to explain the toxic effects mechanisms. The aim of the current work is to explain the toxic effect mechanisms of boron and boron compounds on body systems.

Keywords: boron, boric acid, bortezomib, toxicity

1. Introduction

Boron (B) is an essential element for living organisms. B has different physiological effects on living organisms at low concentrations, whereas it has toxic effects at higher concentrations. Generally, B is not found as an element in nature and is commonly found in the form of boric acid, borax, and other complex forms. People are affected by boron:

• By contacting boron minerals in air and water

• Drinking and using the underground and surface waters in the basins rich in boron deposits

• Taking foods and drinks with high boron concentrations

• Working in quarries and factories

• Working in places that make cleaners and whiteners such as soap, detergent, beauty products, and similar products, or using such products
Since boron is ubiquitous, it will be accepted that no limit can be drawn for being under the influence of boron [1].

Animals and humans could be ingested higher levels of B through foods or may be exposed to boron due to occupational conditions as inhalation, dermal or oral exposure. During the exposure, damaged and injured absorption sites can lead to increased absorption. In some cases, dermal higher exposures to B could result in death. Boric acid could be fatal after higher ingestion [2, 3]. More studies are needed about the cellular toxicity mechanisms of B and B compounds at tissue level. Higher B exposure could cause:

- Mortality risk increase
- Osteoporosis
- Cognitive dysfunctions
- Cell injury
- Inflammation tendency
- Congestion
- Dermatitis
- Renal cells degeneration
- Edema
- Eye irritation
- Intestinal apoptosis
- Developmental toxic effects
- Reproductive dysfunctions
- Cardiovascular dysfunctions
- Data on carcinogenicity are unclear. There were not sufficient data about carcinogenic effects of B and B compounds (Table 1) [4].

As a normal consequence of boron uptake from food and drinking water, human tissues and body fluids contain B. Boron found in soft tissues is close to the blood level. B can accumulate in bones. Muscle tissue, heart, lung, and intestine contain lesser amounts of boron [6, 7]. The World Health Organization compared the blood levels of ingesting boron through drinking water and diet in humans and rats. The distribution of boron in blood and tissue samples for human and rat species, boron kinetics may be the same for both species [8].
Numerous studies on humans and laboratory animals have revealed that more than 90% of borates taken into the organism are removed from the organism in the form of boric acid. It has been reported that boric acid can form complexes with different biological molecules depending on the dose [9].

Regardless of the route of its uptake into the organism, the elimination of boron mainly occurs by glomerular filtration. Glomerular filtration is 3–4 times faster in rats than in humans, and it has been reported that more than 90% of boron, which is taken into the organism by various ways in humans, is removed through urine within the first 24 hours [10, 11].

The data obtained from animal studies are not enough for determining the Bor's potential of causing cancer to human [12]. Boron was not evaluated as a carcinogen by EPA (US Environmental Protection Agency) and NTP (US National Toxicology Program), IARC (International Agency for Research on Cancer) [8]. The studies about boron and its compounds mainly focus on their toxicologies. In the studies about boron exposure, data are stated as equivalent of boron for providing compared data. Under the physiological pH conditions, borate salts are completely converted to boric acid; based on this, it was stated that boric acid and borate salts have similar toxicological properties [13].

In this chapter, we aimed to review current toxicity data of B, and B compounds.

### 2. Boron and boron compounds

Boron (B) as a metalloid belongs to third group of periodic table. Boron has an interesting unique and complex chemical structure like metal and nonmetal. It has very small atomic size as 4.39cm³/mol. B includes three valance electrons, and its ionization energy is very high. B's p-orbital includes vacant electron at B⁺³ state. B has high potential to make anionic complexes than cationic complexes. B occurs in the nature as borates (such as borax Na₂B₄O₇•10H₂O), boric acid [B(OH)₃] or H₃BO₃, and BF₄ (not very common). In living cells, B occurs in the cytoplasm as H₃BO₃ and borate

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose/concentration</th>
<th>Toxic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boric acid</td>
<td>3–6 gr-infants</td>
<td>Nausea, vomiting, greenish diarrhea, dehydration, hypotension, metabolic acidosis, oliguric renal failure, erythematous rash</td>
</tr>
<tr>
<td>Sodium borate</td>
<td>10 mg/kg day and &gt;15 mg/kg</td>
<td>Sex hormone decrease, globulin binding (SHGB) decrease, irritability, disturbed sleeping, vomiting, severe diarrhea, seizures, anemia and death</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>&gt;1.3 mg/ day</td>
<td>Peripheral neurotoxicity and lung toxicity</td>
</tr>
<tr>
<td>Dimethylamine borane</td>
<td>&quot;occupational exposure&quot;</td>
<td>Dizziness, nausea, diarrhea, cognitive dysfunction, slurred speech, irritability, ataxia, peripheral neuropathy, cerebellar damage and parkinsonism. Myelin and axonal degeneration</td>
</tr>
<tr>
<td>Boromycin</td>
<td>&quot;in vitro study&quot;</td>
<td>Hemolysis</td>
</tr>
</tbody>
</table>

Adapted from [5].

Table 1. Boron compounds and toxic effects.
forms. Boric acid and borate interact with several different molecules very easily and form different esters and generate mono-, di, poly hydroxyl forms. Boric acid has affinity to furanoid rings of sugars, which are very important for life. These complex compounds are very important during evolution because of providing organisms stability and very strong defense mechanisms.

B’s inorganic form is originated from anthropogenic sources in the nature and could found elsewhere in soil, water, and atmosphere. Also it circulates in the air, volcanos, ocean, geothermal water sources, etc. According to EPA (1987), boron compounds are released into the air as anthropogenic sources. Generally, because of boron dust, people are exposed to boron via the air in boron mines. A dose of 14 mg of boron per cubic meter of air has been reported in boron mines where boric acid and refined products are produced. Boron can be found in soil, especially in the form of bonk JMI or borate, absorbed on soil particles, or in soil solution as a free anion. In the research studies, it has been shown that the amount of boron in the plant is primarily related to the soil pH. Other important factors are the plant type, the boron content of the soil, the type of ions that can change in the soil, the amount and type of other minerals in the soil, the amount of organic matter in the soil, the temperature of the soil, the wetting and drying conditions of the soil, the soil-water ratio, the light intensity, and genetic factors. Low-boron soils contain up to 0.7 ppm boron and do not pose a problem for any plant. Medium-boron soils contain 0.7–15 ppm boron, and it has been determined that it does not cause problems for some plants. Soils with high boron contain 15–75 ppm boron and are mostly dangerous for plants, while soils with very high boron contain more than 75 ppm boron, and these are dangerous for plants. Boron has important metabolic functions in plants and plant growth stops in the absence of boron in the soil. Boron shows its effects on drinking water and agricultural water. In 1968, the Water Quality Criteria Committee set the limit value as 1 mg/l; in 1971, as a result of the investigations of the Drinking Water Standards Technical Review Committee, it was decided that there was no evidence to require the 1 mg/l limit, and that 0.3 mg/l was a reliable limit for human health. According to research studies, it is important for human health that drinking water does not contain high levels of boron [14, 15].

The negative effects of boron products on the environment are much lower than in other industrial sectors. In fact, with the effect of radioactive substances after chemotherapy, it is one of the elements that can be considered environmentally friendly due to its necessity for human and living creatures [16].

Depending on the technological developments, the economic grades of the ores are reduced with the development of new methods and equipment, and many stored heaps in the form of waste are evaluated in this way. Accordingly, possible evaluation possibilities in the future should be considered in the disposal of waste. For these reasons, it is necessary to pay maximum attention to the storage of boron wastes. It is possible to list the advantages to be obtained as follows [16].

- The problems arising from the stocking of wastes and the cost of stocking will decrease.
- Environmental pollution will be minimized.
- An additional income will be obtained with the new product produced.
- It will be prevented that the wastes pollute the underground and surface waters.
Predominant mineral sources of B are found in Australia, China, Turkey, Russia, and Argentina. B and boron compounds could not naturally occur as volatile compounds; however, minimal volatile boron compounds release to atmosphere via volcanic activities and different industrial places. B is an essential for several body organs and systems, and 1–13 mg/kg consumption is acceptable. High exposure could cause several health disorders in neurological, urogenital, skeleton, and cardiovascular systems [17].

3. Respiratory system

There are few studies on the effects of boron and its compounds on the lung. In some studies, it has been reported that exposure to boron may cause damage to the lung cellular layer. It causes symptoms such as irritation in the nasal epithelium, nosebleeds, cough, and shortness of breath in people working in boron mines [18]. Boron nitride nanoparticles (BNNTs) appear as a nanotechnological product with a wide range of applications in engineering and biomedical fields. Therefore, there is an increasing interest in studies on the risks these products may pose for health. It has been demonstrated that BNNTs cause cytotoxicity in human lung adenocarcinoma epithelial (A549) cells and murine alveolar macrophage cells (RAW 264.7), being concentration dependent (0.02, 0.2, and 2 μg/mL concentrations). In addition, cytomorphological examinations revealed serious cell morphology disorders in both cell types [19]. In another study, it was shown that high boron application may cause an increase in the capacity to transform in non-tumorogenic cells. In total, 5–50,000 μM concentration range of boric acid is applied to human nontumorigenic lung epithelial (BEAS-2B) cells and human lung epithelial carcinoma (A549) cells. It has been determined that 5000–50,000 μM concentrations significantly suppressed the anchorage-dependent growth of cells. This effect could have occurred via an important pathway that plays key role in cell transformation such as SRC and PI3K/AKT and MEK/ERK signaling pathway [20]. Diborane gas (B2H4) is a strong toxic substance for the respiratory tract. Mice were exposed to diborane gas at a concentration of 5 ppm diborane (1.7 mg boron/m3) for 2 weeks, which caused severe damage to their lungs, including pulmonary congestion, hemorrhage, and edema. Mild changes such as infiltration of polymorphous neutrophils in the peribronchiolar region were observed in the group given 0.7 ppm diborane (0.2 mg boron/m3). Case reports have stated that boron can be lethal after short-term oral exposure at high doses and can be quite large despite variability in human responses to acute exposure. It has been reported that the minimum lethal dose of boron (as boric acid) taken is 2–3 g in infants, 5–6 g in children, and 15–20 g in adults. However, 784 cases with boric acid (10–88 g) reported no deaths, of which 88% of the reviewed cases were asymptomatic. Liver, kidney, central nervous system and gastrointestinal effects, and skin lesions have been found in fatal cases following boron ingestion, but death has been attributed to respiratory failure [21].

4. Immune system

If boron levels decrease in body, this decrease causes immune deficiency. However, higher and/or chronic exposure could have negative effects on immune system homeostasis [4].
Jin et al. conducted a study that showed that the effect of boron on the immune system in vivo is dose-dependent. They supplemented 0, 20, 40, 80, 160, 320, and 640 mg/L B in drinking water of rats (1.5, 3, 6, 12, 24, 48, and 96 mg/kg/bw) for 70 days. It was demonstrated that 20 and 40 mg/kg doses of B improved immune functions in the rats and increased the concentrations of serum IgG levels, splenic IFN-γ and IL-4 expressions, and the expression levels of CD3+, CD4+, and that they also proliferated cell nuclear antigen (PCNA) + cells. However, at such high concentrations as >48 mg/kg/bw, toxic effects on immune system were detected and immune activities were suppressed. At higher concentrations of IgG, IL10 levels and CD8+ cells were significantly found as decreasing. This is a good example of U-shaped dose-response effect. Both very low and very high concentrations could be associated with harmful effects on immune system [22].

Boron nitride nanotubes (BNNTs) engineered nanomaterials have superior electrical, chemical, and thermal properties, and they were planned to be used in the area of engineering applications such as lightweight and high-temperature ceramic components, flame retardants, etc. BNNTs’ size could be <100 nm in diameter and microns of length. Effects of mixture of BNNTs (BNNT-M) in vitro in THP-1 cells (human peripheral blood monocyte cell line) and in vivo pathogen-free, male C57BL/6J mice were evaluated by Kodali et al. The range of in vitro concentrations was 0–100 mg/ml and in vivo dose was 40 μg/mouse. BNNT induced cytotoxicity and cellular oxidative stress in THP-1 cells, being concentration-dependent. These results were in accordance with in vivo in the same study as increased lactate dehydrogenase levels in bronchoalveolar lavage, mitochondrial membrane potential loss. They demonstrated that cathepsin B, caspase 1, protein levels of IL-1b and IL-18 increased both in vitro and in vivo. These results indicated that BNNTs could increase acute inflammation and toxicity in vitro and in vivo [23].

The use of borax (Na2B4O2(H2O)10) as a food additive and its excessive consumption in recent years could result in serious toxic effects such as kidney damage. Higher borax exposure decreased immune cell numbers and increased sister chromatid exchange in blood immune lymphocyte cells [24].

5. Nervous system

Bortezomib (C19H25BN4O4), or dipeptidyl boronic acid, is a proteasome inhibitor drug used in chemotherapy against hematologic malignancy. It has an anticancer activity. However, bortezomib often causes severe peripheral neuropathy. This condition has a special name such as “bortezomib-induced peripheral neuropathy (BIPN).” BIPN includes numbness and painful paraesthesia. Bortezomib has toxic effects on dorsal root ganglia via endoplasmic reticulum stress, protein carbonylation, and oxidative stress inducing. It also causes morphological changes in nervous system cells such as microglia [25, 26].

It was determined that infants exposed to 5–14 g boric acid or sodium tetraborate exerted such serious neuronal symptoms such as headache, tremor, convulsions, and even death after coma. These symptoms were associated with neuron degeneration, edema, and hemorrhage in the brain. However, chronical B deficiency causes such mental disorders as focusing problems, electroencephalogram changes, vigilance and psychomotor activity problems. B deficiency is strongly related to nervous system action potential problems [27]. In another study, Ozansoy et al. demonstrated that sodium borate decahydrate and boric acid administrations improved amyloid-beta
toxicity in SH-SY5Y cells in vitro via increased expression levels of Sirt1 and regulated GSK-3α/β expressions [28]. Thus, this information suggested that B and B compounds could have U-shaped effects in the nervous system. Excessive B and B compounds exposure causes toxicity, and deficiency causes neuron metabolic pathway problems, and even B and B compounds could be possible therapy options for neurological diseases.

6. Reproductive system

It is well known that boron has negative effects on male and female reproductive system. It causes atrophy in seminifer tubulus, germ cell loss, sperm mobility impairment, altered follicle stimulating hormone and testosterone, reduction of ovulation processes [4]. Exposure to a range of boric acid concentrations between 1000 and 9000 ppm causes serious male fertility problems such as testicular atrophy and decreased sperm motility in experimental animals. With the studies on different species of animals, these toxic effects were confirmed with different doses. Human studies with occupational workers in Turkey and in China did not confirm these results [29, 30]. As a result of a study conducted in Russia, it was determined that sexual activity decreased in boron workers (n = 28). In addition, interestingly, in the study conducted on boron workers in the United States, it was determined that there was an increase in the birth of girls compared with boys [7].

According to animal studies, it was reported that boron, boric acid, and sodium borate compounds could be toxic to reproductive system and also developmental system. For reproductive system, NOAEL levels of boron were 17.5 mg /kg/day and for developmental issue NOAEL levels of boron were 9.6 mg/kg/day. Duydu et al. reported that daily 14.45 ± 6.57 mg/day boron exposure in boron workers did not lead to any change in reproduction-related hormone levels (FSH, LH) and sperm cells morphology and count [31].

In different studies, it was shown that low levels of boron compounds caused developmental problems. Low levels disrupted developmental processes of chicken (400 mg B/L drinking water), rat (640 mg B/L drinking water), and African ostrich (640 mg boric acid/L) experimentally. In another study, boric acid exposure higher than 0.5 mmol/L in male rats’ Sertoli cells triggered necrosis and apoptosis and caused a decrease in cell viability rate. At 40 and 80 mmol/L boric acid levels, it was reported that sertoli cell viability was arrested at G0/G1 phase [32].

In one lineage study, male rats were exposed to boron via oral gavage with different concentrations. Then they mated with unexposed female rats. It was observed that fetus viability rate decreased at higher exposure levels (100 mg B/kg/day) and fetus malformations increased at higher concentration. Additionally, testicular enzyme levels (MDH, SDH, G3PDH) and FSH levels changed. These changes were associated with lipid metabolism changes that play a key role in hormone and enzyme activities via metabolomic assays [33].

7. Cardiovascular system

There are many studies showing that the inclusion of boron and boron compounds as food supplements has a positive effect on the cardiovascular system. It has been reported that it will reduce especially cardiovascular risk factors. Today, however,
The Toxicity of Environmental Pollutants

the production and use of boron-containing compounds for the treatment of various diseases are popular. Some of these compounds have been reported to cause cardiovascular toxicity in toxicity studies. Boron nitride (BN) nanoparticles and different formulations could be good candidates for biomedicines. Liu et al. reported that BN nanoparticles coated by PEG (BN-PEG) highly were distributed in the heart tissue and caused high toxic effects histopathologically [34–36].

Hexagonal boron nitride nanoparticles (hBNNPs) are nanomaterials that have special chemical properties and candidate therapeutics in medical applications. In Wistar albino rats, it has been determined that hBNNPs increased oxidative stress. In the cardiac tissues, 3200 \( \mu \)g/kg dose of hBNNPs caused a statistically more significant increase in LOOH levels than the controls [37].

It is known that Bortezomib leads to neurological disorders as peripheral neuropathy; however, a study conducted with Bortezomib showed that it decreased the left ventricular ejection fraction, led to cardiomyocyte abnormalities, damaged the cardiomyocyte contraction through decreased ATP [38]. In another study that compared Boronic acid and Epoxyketone Proteasomal-Targeted Drugs found that boronic acid was much more damaging to myocyte [39].

8. Anticancer boron compounds

Cancer is the disease that reduces the life quality of patients the most and causes the highest rate of death in the world. For this reason, intensive scientific research continues on strategies that will both improve the quality of life of patients and treat the disease. Boronic acid, bortezomib, talabostat, and boron nitride capture therapy are important boron-containing candidates for anticancer therapy. Bortezomib is a 26S proteosoma inhibitor and activates NF-\( \kappa \)B. This process enhances apoptotic mechanism in the cells. Boronic acid is used as an anticancer agent via ROS modulation in the cells. It has been demonstrated that boronic acid prodrugs significantly induce apoptosis in primary leukemic lymphocytes [40]. Bortezomib was approved by US Food and Drug Administration (FDA) in 2003, and at the present time, it is used for chemotherapy of multiple myeloma and mantle cell lymphoma, but peripheral neuropathy is one of the common adverse effects of Bortezomib [41].

9. Conclusions

Boron is a vital element for living organisms. Boron and several types of its compounds have different beneficial effects in humans at sufficient doses. However, too little or too much intake in the required amount causes serious health problems. Its use as a food supplement to prevent boron deficiency in the body has become popular today. In addition, the use of boron and its compounds in many fields such as cosmetics, cleaning, medicine, electronics, war industry, and the development of new products for these fields are increasing day by day. Such reasons cause an increase in exposure not only to individuals working in boron mines, but also in daily life. Besides, boron and its compounds appear as candidate molecules in the treatment of various diseases. All of these factors indicate that there will be more exposure to boron and its compounds today and in the future. For this reason, it is a fact that these compounds, which are mentioned as having many benefits under normal conditions, will also encounter toxic effects due to the increased exposure over time.
It is also possible that some boron-containing compounds can be candidates for cancer treatment through their structural effects and cytotoxic effects on cellular mechanisms. This shows the importance of toxicity studies of these compounds at all times. However, developing scientific technologies will also enable these effects to be minimized.

Conflict of interest

The authors declare no conflict of interest.
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