Effect of Boron on Human Health

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Abstract: Studies on boron, its mechanism and health effects are growing although the safe limits of daily boron exposure have not been clarified. Current knowledge about the toxic levels of boron on humans is not sufficient and needs to be improved. The main toxic effect of boron in animals involves the reproductive system, including specific adverse effects in the male reproductive tract in rats, mice and dogs. Boron determination in biological matrices needs sufficiently sensitive procedures for detection at trace levels, and many techniques do exist. In this paper, we reviewed the general view of potential impact of boron on health, exposure of boron and its determination techniques.

Keywords: Boron determination, exposure, reproductive effect, beneficial effect, daily intake, risk assessment.

1. BORON AND ITS DETERMINATION METHODS

Boron (B) is a non-metal element in Group 13 of the Periodic Table. Properties of B are very close to carbon and silicon. This element has one less valence electron than valence orbitals. Due to small size and high ionization energies, boron results in covalent bonding rather than metallic bonding [1]. B is a rare element in the Earth, representing only 0.001%. It is estimated that worldwide commercial borate deposits are 10 million tonnes [2]. In the Earth, B is not present in the elemental form. It is found in the form of borax, boric acid, colemanite, kernite, ulexite and borates [3]. There are two forms for elemental boron, namely amorphous boron, which is a brown powder, and crystalline boron, which is dark grey in color and a semiconductor at room temperature. In elemental form boron reacts with gaseous HF to form a volatile BF_3, however it does not react with gaseous HCl, HBr or HI [4]. Crystalinity, particle size, purity and the medium temperature are some of the factors that affect the oxidation of boron. For example, B does not react with air at room temperature, however it forms B_2O_3 (s) at high temperatures. In 1824, the first boron compound was synthesized by Jöns Jakob Berzelius [5, 6]. Many boron compounds with different metals and nonmetals are used in industry, such as detergent production, glass and ceramic manufacture, agriculture and textile [7]. It also has application in the semiconductor industry. Boron is added to pure semiconductor materials such as silicon, germanium and silicon carbide in small amounts to alter its conductive properties for use in transistors and diodes. Having one less valence electron than the host atom, it results in p-type conductivity. Solid (B_2O_3), liquid (BBr_3) or gaseous boron sources (B_2H_6 or BF_3) have been widely used to introduce boron into semiconductors [8].

Determination of boron requires sufficiently sensitive procedures for detection at the μg L^{-1} or lower levels. In literature, there are many techniques reported for the quantification of boron in different matrices. Spectrophotometric determination of this element has been commonly employed. Spectrophotometric methods based on the usage of different chemicals such as carminic acid [9], curcumin [10], quinalizarine [11] and azomethine-H [12, 13] have been applied to determine boron in a varety of matrices. Among all these reagents, azomethine-H has been most widely utilized. This method is not only fast, simple and sensitive, but also does not require concentrated acids [14]. In the spectrophotometric methods, boron in sample is converted to boric acid or borates. Produced forms of boron react with the chemicals cited above in mostly acidic solutions to give a colored boron-chelate complex [15]. Spectrofluorimetry is another sensitive technique for boron determination where complexes of B are formed and their fluorescence intensity is measured at a specific wavelength. Different complexing agents have been applied for the fluorometric determination of boron. Resacetophenone is one of the reagents used for this purpose. Boron gives of a blue fluorescence with resacetophenone in a sulphuric acid or phosphoric acid medium. The main advantages of this method are sensitivity and short reaction periods [16]. Mir *et al*. used 2-(2-hydroxybenzylidenimine) benzene-arsonic acid (HBBA) as a reagent for the fluorimetric determination of boron. In the medium of 85% w/w sulphuric acid, complexing agents react with boron. After heating at 90 degrees for 45 min a fluorescent compound was formed. The detection limit of the method was 0.01 μg/mL. The linear calibration range was found to be 0.1–8 μg/ml in the solution [17]. Potentiometry is another technique for the determination of boron; the main advantage of potentiometry is the elimination of possible interferences

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by separation of boron from matrix [18]. Determination of boron in silicon was performed by Lanza and Buldini using the potentiometric method. In this study, silicon was dissolved using hydrofluoric acid and ammonium fluoride in the presence of hydrogen peroxide: boron was then converted to fluoroborate ion. An Orion fluoroborate-selective electrode was used to measure fluoroborate activity [19]. Ramirez-Ortega *et al*. used a carbon paste electrode modified with a β-Cyclodextrine-Azomethine-H inclusion complex for the potentiometric determination of H_3BO_3 in aqueous solution; in this study, Azomethine-H plays the role of recognition agent for H_3BO_3 [20].

Determination of Boron by atomic emission spectrometry (AES), measuring boron oxide emissions, has been performed using different types of flames. In general, this method has low sensitivities and suffers from interference problems [21]. Some separation and preconcentration methods combined with AES have been used to overcome these problems [22, 23]. Among all atomic spectroscopic techniques, inductively coupled plasma atomic emission spectrometry (ICP-OES) [24, 25] and electrothermal atomic absorption spectrometry (ETAAS) [26, 27] have some problems such as spectral interferences, memory effects and insufficient sensitivity for the determination of boron in trace levels [28]. Inductively coupled plasma mass spectrometry (ICP-MS) is another popular spectrometric technique for boron determination which is preferred to ICP-OES because of higher sensitivity, lower detection limits and multielement analysis capability with a high speed scanning. Although this technique has very low detection limits, it suffers from the blank problem caused by glass and/or quartz parts of instrument including, nebulizer, spray chamber and torch. In ICP-MS instrument, it is possible to monitor both isotopes of B, namely ^{11}B and ^{10}B. Hence, the isotope dilution method, the most precise approach in the quantitative determinations, can be easily performed using ICP-MS [29]. ICP-MS has been used for the determination of boron in many matrices including high-purity quartz [30], iron and steel with isotope dilution [31], body fluids with isotope dilution [32]. Serious memory effects and matrix interferences are some of the problems found in the use of ICP-MS in boron determination. Internal standardization should be used to control drift and signal fluctuations [28]. Although ICP-MS has very low detection limits it is not commonly used for boron determination owing to its high cost. Hence, many researchers prefer other techniques because for economical and practical reasons.

2. BORON EXPOSURE

Boron is absorbed almost completely by gastrointestinal and respiratory systems and mostly present in body tissues and fluids as Boric acid $B(OH)_3$ and in lesser amounts as $B(OH)_4^-$ anion [33]. Boric acid is known as a natural compound and it is taken from water, vegetables and many other foods through diet [34]. In many populations food ingredients [35] and occasionally drinking water are the major source of boron intake.

The amount of boron intake by people is dependent on the types of food consumed [36]. Food stuffs such as fruits, vegetables with leaves and legumes contain relatively high amounts of boron. Boron concentration in meat, fish and dairy food products is not high. Coffee and milk contain low amount of boron. However, in populations with high coffee consumption this beverage can be a major sourse of boron intake . Hazelnut butter, avocado, vine, peanuts and other nuts with shells have high amounts of boron [37]. According to WHO (World Health Organization), it is expected that the amount of boron taken is 0.44 μg /day *via* air, 0.2-0.6 mg/day *via* drinking water and 1.2 mg/day *via* diet [38].

There is no information about boron content of food products in many countries. Hence, the amount of boron intake *via* diet is scarce. According to Rainey *et al.* [39], the average boron intake for adult-men in the US, Germany, England, Mexico, Kenya and Egypt was calculated as 1.11 ± 0.69, 1.72 ± 0.47, 1.30 ± 0.63, 2.12 ± 0.69, 1.95 ± 0.57 and 1.31 ± 0.50 mg/day, respectively. In addition, for adult-women in the US, Germany, England, Mexico, Kenya and Egypt, average boron intake was 0.89 ±0.57, 1.62 ± 0.76, 1.14 ± 0.55, 1.75 ± 0.48, 1.80 ± 0.49 and 1.24 ± 0.40 mg/day, respectively. Korkmaz *et al*. calculated the average boron intake of people who live a place where the boron concentration in drinking water is higher than 2.0 mg/L. In this study, 66 men were taken into consideration. According to this study, average boron intake for men who work in boron rich areas was calculated as 6.77 mg/day while this value was 1.26 mg/day for the control group [40].

Boron intake varies with human metabolism and age. For instance, boron intake is 0.75 ± 0.14 mg/day for infants of 0-6 months, 1.34 ± 0.02 mg/day for men of 51-70 years old, 1.39 ± 0.16 mg/day for nursing mothers [41].

Boron taken orally was completely absorbed by the gastrointestinal system of rats, rabbits and human beings over a very short period of time [41]. Absorption of boron orally is very similar in both humans and animals [36]. Studies have shown that boron is also absorbed through inhalation exposure [42, 43]. Culver *et al.* reported that total estimated boron intake including both diet and environmental exposure had for the high-borax dust exposure group a mean daily boron intake of 27.90 mg/day [42]. In addition, it was determined that boron was absorbed by healthy skin only to a very limited extent [44], although absorption of boron that is present in liquid solution occurred in irritated skin [45]. Distribution of boric acid in human tissues is similar to that of animals. Boric acid that is consumed by human and animals is quickly distributed to body liquids [45, 46].

3. BORON TOXICITY

Current knowledge about the toxic level of boron in humans needs to be improved. The limited data on this topic has only been obtained from human poisoning cases and toxicity studies on animals. Based on these reports, data from accidental poisonings indicate that the acute lethal dose of boric acid is 3000-6000 mg for infants and 15,000-20,000 mg for adults. Clinical effects include irritability, seizures and gastrointestinal disturbances. There have also been reports of inflammation, congestion, exfoliation of the mucosa, exfoliative dermatitis, findings of cloudy swelling and granular degeneration of renal tubular cells and oedema. Clinical symptoms of boron toxicity have been reported within the dose range 100 to 55,500 mg depending on age/body weight. Inter-individual variability appears to be high [47].

Risk assessments of boron indicate no significant risk of toxicity to humans at currently estimated dietary or municipal drinking water levels of exposure but boric acid and sodium borates have low acute toxicity. They are not skin irritants, nor skin sensitizers. Some sodium borates cause eye irritation in animals, but 50 years of occupational exposure revealed no adverse ocular effects in humans [48]. Boron compounds are toxic to all species tested at high doses, but they are not mutagenic or carcinogenic. The major chronic toxicities are developmental and reproductive [49].

To our knowledge, no epidemiological studies are available regarding the effects of boron on the development of the human fetus. Experimentally, fetal toxicity was observed in mice, rats and rabbits. The average fetal body weight was significantly reduced in a dose-related manner in all exposed groups compared to controls. The reported developmental toxicities occuring after boron exposure include high prenatal mortality, reduced fetal body weight, cardiovascular system, central nervous system, malformations of the eyes, cardiovascular system, and axial skeleton. There is no data in particular regarding the ability of boron to cross the placenta or accumulate in fetal tissues [50-52]. However data from animal studies suggests that developmental toxicity may be an area of concern in humans following boron exposure.

In animals, the main toxic effect associated with boron involves the reproductive system. Boron caused specific adverse effects in the male reproductive tract in rats, mice and dogs, including shrunken scrota, inhibited spermiation, degeneration, and atrophy of seminiferous tubules, with an absence or loss of germ cells. Boron also caused a reduction in ovulation in female rats and renal lesions in female mice [49].

Ku *et al*. orally administered rats 0, 3000, 4500, 6000, and 9000 ppm (0, 26, 38, 52, and 68 mg B/kg/day) for 9 weeks to compare the relationship between development of lesions and different boron concentrations. They found that sperm production was inhibited at dosses of 3000 and 4500 ppm, while doses of 6000 and 9000 ppm caused atrophy. It was reported that an average of 5.6 μg B/g boron concentration in testis tissue inhibited sperm production, while 11.9 μg B/g level resulted in atrophy. The NOAEL for this study was reported as 26 mg B/kg/day [53]. Following this study, the same researchers treated testis cells *in vitro* with 11.9 μg B/g. In this study it was observed that boric acid negatively affected the production and maturation of germ cells at early stages [54].

In addition to these studies, Şaylı *et al*. interviewed 927 subjects (230 female, 697 male) randomly selected from six different areas in the provinces of Balıkesir, Kütahya and Eskişehir, the highest known boron deposit areas in Turkey. These people were exposed to boron either environmentally or occupationally, or both. No evidence was found to suggest that boron interferes with human fertility and reproduction [55]. In a study completed with a highly exposed population in Turkey, where exposure occurs mainly from naturally high levels of boron in drinking water (up to 29 mg B/l) as well as from mining and production, no adverse effects were reported on fertility over three generations [56-58]. Similarly, Whorton *et al*. standardized birth-ratio study of male workers exposed to sodium borate dust at levels of 10 mg/m^3 of air. This study showed no evidence of any exposure-related effects on fertility [59]. The data of Moore *et al*. on human studies are insufficient to determine whether boron exposure may cause toxicity on male or female reproduction [60]. Whorton *et al*. found a statistically significant increase in fertility as measured by live births among the employees of the inorganic borate facility. Boron does not appear to be causing any decrease in fertility due to exposures either as analyzed by the borate exposure categories or over time, which is an indirect measure of exposure. A non statistically significant increase was detected in the percentage of female offspring. This increase was not due to a deficiency of male offspring, but rather to a marked increase in the numbers of female offspring. This increase in the percentage of female offspring does not appear to be related to exposures to inorganic borates. Based on the data, exposure to inorganic borates does not affect fertility adversely in this population. Reproductive effects of sodium borates on occupationally exposed male employees at a large mining and production facility were investigated in the Mojave Desert of California. Under the conditions studied, there were no adverse reproductive effects of high borate doses, similar to reports from oral ingestion studies in animals [61]. In a study on the employees of boron industry in China, it was figured out that occupational exposure to boron did not have a significant effect on the sperm density of employees [62]. In addition, some papers have currently published in this field to make risk assessment of boron [63, 64].

Overall, the claims that boron cause infertility are only supported by animal toxicity studies, which employ higher concentrations of boron than the levels of environmental or occupational human exposure as shown by the epidemiological studies.

4. BENEFICIAL EFFECTS

Boron is a trace element playing an important role in mineral and hormonal metabolisms, cell membrane functions, and enzyme reactions. Boron also affects osteoporosis, heart trouble, paralysis, diabetes and senility [65]. Boron is involved in calcium and bone metabolism. Experiments with boron supplementation or deprivation show that its effects are more marked when cholecalciferol and magnesium are deficient. Boron may be involved in cerebral function due to its effects on the transport across membranes. Boron is involved in the synthesis of extracellular matrix and is helpful in wound healing. Compounds of boron have been shown to be potent anti-osteoporotic, anti-inflammatory, hypolipemic, anti-coagulant, and anti-neoplastic agents both *in vitro* and *in vivo* in animals [66].

Experimental studies show that boron has protective characteristics against prostate cancer [67]. Boric acid in low concentrations partly suppresses the prostate specific antigens (PSAs) proteolytic activity. Therefore, boron compounds can be used for regulating PSAs activities. Furthermore, the suppression of PSA activities caused by boron can help prevent the increase and development of prostate carcinoma [68]. Boric acid concentrations ranging between 60-100 μM suppress reproduction of cells in prostate cancer's cell line [69]. In DU-145 prostate cancer cell lines, depending on dosage in 0-1000 μM BA application, a decrease in cell proliferation was observed [70]. A research undertaken

in Texas, USA showed that B concentrations in underground water and the incidents of prostate cancer and mortality rates have an inverse correlation [71]. Boron's effect on lung cancer is not clear, but there has been evidence pointing to boron's antioxidant and anti-inflamatory characteristics [72]. In research undertaken by Korkmaz *et al*., cervical smear samples were taken from women of poor social backgrounds. 587 and 472 women across boron-poor and boron-rich areas took part respectively. While no cytopathologic evidence of cervical cancer was observed in women living in boron-rich areas, for 15 women from boron-poor areas cytopathologic evidence of cervical cancer was observed [73]. Dietary intake of boron can play a role in reducing plasma lipids. The impact of dietary boron intake on important metabolic processes like coronary heart diseases, arthritis and osteoporosis is also supported with evidence. Boron, by reducing the making of some steroid hormones, can prevent these chronic illnesses. When the amount of Boron increased in the diet of humans, it was demontsrated by some researchers that estrogen, testosterone and plasma ionised calcium levels increased and the negative impacts of the calcium disposal and vitamin D and magnesium deficiencies were lessened [74].

Studies confirm that boron can have an impact on brain functions and the cognitive performance of humans [75]. Boron can also play a vital role in bone development, "inflamatory response" and central nerve system functions. In cases of boron deficiency, bone volume and trabecula thickness shrink, and trabecula seperation increases. Evidence from deficiency studies show that some animals, in order to complete their life cycle, need boron, and very low amounts of boron intake can cause bone health to deterriorate, brain functions and immune "response" to weaken [76, 77]. Evidence from more recent studies proves that boron supports the immune system [78].

Taking the lack of epidemiological evidence into consideration, WHO (World Health Organization) put boron in the possible essential elements category. This could be a sign that with the increasing number of studies, from a nutritional point of view it may prove to be an essential element. In light of the evidence above, provided that no toxic level of exposure is present, boron shows signs that it could make positive contributions to human health.

It is clear that any studies about reproduction toxicology are very important for the assessment of daily boron intake. Hence, researchers should focus on this topic to improve the knowledge about boron-human health relations.

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