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EDITORIAL

Boron and its compounds: current biological research activities

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Boron is a ubiquitous element, appearing in rocks, soil, and water. Major exploitable deposits are found in arid areas with a history of geothermal activities, namely in Western Anatolia (Turkey), the Mojave Desert (California, USA), and the Liaoning province in northeastern China. Apart from classical applications of boric acid and its salts in detergents and bleaches, production and use of boron compounds have increased steadily over the last decades, mainly for the production of thermal shock-resistant borosilicate glass and fiberglass (Woods 1994). With increasing use of borates, regulatory issues have been raised related to boron in drinking water (Murray 1995), cosmetic products (Platzek et al. 2010; SCCS 2010), toys (Craan et al. 1997), etc. An important issue is the European REACH legislation (see Degen and Hengstler 2008; Duydu et al. 2016).

Against this background, the numbers of articles in scientific journals on biological effects of boron have increased steadily since 1990 (Farfán-García et al. 2016), and important contributions were published in this journal. Important clusters of contemporary research can be identified in (1) the essential role of boron in plants and animals and associated mechanisms of action, (2) perspectives for boron compounds in pharmacy/pharmacology, and (3) human safety aspects. These developments appear interconnected to some extent, as there may be bridges in the molecular modes of action. In total, matters of risks and benefits of boron compounds receive increasing attention (Pizzorno 2015).

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Role of boron compounds in plants

Boron appears to be a micronutrient in animals and humans (Nielsen 2002; Pizzorno 2015), and the World Health Organization has classified boron as being "probably essential" for humans (Del Rosso and Plattner 2014). However, the major driving force for research on the biological essentiality of boron is in plant science. It has been recognised soon that boron is an essential element in plants and a number of other organisms (Tanaka et al. 2010). The breakthrough for plant boron research was the discovery that boron stabilises plant cell walls by cross-linking rhamnogalacturonan II through ester bonds with *cis*-diol groups of sugar moieties. Thus, boron is important for architecture and stability of plant cell walls (Bolaños et al. 2004; Matthes and Torres-Ruiz 2017). Other research milestones included the identification of a boric acid channel, NIP5;1, and a boric acid/borate exporter, BOR1, from *Arabidopsis thaliana* (Takano et al. 2008). There is increasing evidence that the boron transporters are generally important for plant development, for instance in roots and shoot nodes and for the development of inflorescence tissues (Zhang et al. 2017).

A further research focus with the potential for practical applications is the role of boron in signalling mechanisms among bacteria and specifically among legumes and rhizobia leading to nitrogen-fixing symbiosis. Here, the discovery of a boron-containing bacterial signal molecule, autoinducer AI-2, a furanosyl-borate diester, was decisive. AI-2 is produced by several bacteria, and the gene encoding its synthesis is widely conserved.

On this basis, it has been concluded that boron is a dynamic trace element affecting an exceptionally large number of seemingly unrelated biological functions (Bolaños et al. 2004). One common point in the mode of action of a number of boron compounds in biological systems seems to be the stabilisation of molecules with *cis*-diol groups by boron, independent of their specific function.

Therapeutic developments

This builds an immediate bridge to possible therapeutic use of boron-containing compounds. In fact, since the year 2000, the numbers of studies on the medicinal use of boron-containing compounds have by far exceeded the numbers of reports on boron-related toxicity (Farfán-García et al. 2016). For instance, boron-containing structures may influence inotropic and metabotropic receptors, enzyme-linked receptors, and cytoplasmic and nuclear receptors (Soriano-Ursúa et al. 2014). The administration of boric acid to humans in quantities of 20–60 mg/day has been found effective for arthritis treatment (Travers et al. 1990), and specific boron-containing compounds appear to reduce certain types of neoplasia (Scorei and Popa 2010).

As an example, borax (disodium tetraborate) may inhibit the growth of tumour cells. In HpG2 ells, which are susceptible for the anti-proliferative effects of borax, the apoptotic process triggered by borax involves the up-regulation of p53 and the down-regulation of Bcl-2 (Wei et al. 2016).

At present, there are attempts at establishing biological structure–activity relationships of boron-related compounds in different ways, although this avenue of research is still at its beginning (Farfán-García et al. 2016).

Focus of toxicological research

Because of the high p*K*a of boric acid, regardless of the form of inorganic borate incorporated (boric acid, borax, and boron associated with animal or plant tissues), the uptake, distribution, and excretion of inorganic borates in the urine is almost exclusively in the form of non-dissociated boric acid. Because of the absence of metabolism, the toxicokinetics of boric acid are very much comparable across species, including humans (Geldmacher-v. Mallinckrodt and Pooth 1969; Jansen et al. 1984; Murray 1998; Usuda et al. 1998).

Boric acid has been used as an antiseptic. It is acutely toxic after excessive doses; for instance, lethality has been reported in a patient after incidental instillation of 30 g boric acid (Hauck and Henn 1969). Owing to its irritant properties, current occupational exposure limits are based on local sensory irritation to the eyes and the upper respiratory tract (DFG 2011). An irritant to the lower respiratory tract is diborane, as demonstrated in rats (Nomiyama 1995) and mice (Uemura et al. 1995).

A number of in vitro mutagenicity studies were performed with boric acid and its salts, including assays in *S. typhimurium* and *E. coli*, gene mutation tests in mammalian cells (e.g., L5178 mouse lymphoma, V79 Chinese hamster cells, and C3H/10T1/2 cells), UDS in hepatocytes, chromosomal aberration, and sister chromatid exchange studies in several systems, all with negative results (SCCS 2010). In V79 cells, boric acid was even protective against DNA damage induced by lead or cadmium (Ustündağ et al. 2014). As far as humans are concerned, studies of DNA integrity (COMET assay) in sperm cells of boron-exposed workers were negative (Duydu et al. 2012).

A major current focus of toxicological studies on boron compounds is on reproductive toxicology, triggered by EU legislations (Duydu et al. 2016). Earlier animal studies yielded NAOELs for rat fertility and rat developmental toxicity of 17.5 and 9.6 mg/kg b.w., respectively (Weir and Fisher 1972; Price et al. 1996). Based on these data, there was a dispute as to whether boron compounds ought to be categorised as reproductive toxins. This has induced a number of studies in humans.

Scially et al. (2010) compiled studies on nearly 1000 men and women in boron mining or processing in the Liaoning province of China. These included individual assessments of boron exposure, interviews on reproductive experience, and data on semen analysis. No compelling evidence of male reproductive effects attributable to boron could be obtained in highly exposed workers. This was supplemented by a further study of possible interactions of occupational boron exposures and semen quality that again found no significant correlations between blood or urine boron concentrations and adverse semen parameters (Robbins et al. 2010).

Another series of studies into human reproductive toxicity has been performed in boron-rich areas of Turkey with high drinking water levels, without clear-cut effects on reproduction (Şaylı et al. 1998; Korkmaz et al. 2007).

In this journal, a large human study of reproductive effects of boron was published (Duydu et al. 2011). Persons were exposed both occupationally and via drinking water. Unfavourable effects of boron exposure on indicators for male reproductive toxicity (concentration, motility, morphology of the sperm cells, and blood levels of follicle-stimulating hormone, luteinizing hormone, and total testosterone) were not detected.

A comparison was performed of the human exposure levels in the aforementioned studies, based on reported boron blood levels with the experimental NOAEL conditions for reproductive toxicity in rodents (Bolt et al. 2012). In general, high environmental exposures to boron were lower than reported high occupational exposures. The comparison revealed no contradiction between the human and experimental reproductive toxicity data, as it appeared that human boron exposures, even in the highest exposed cohorts, were too low to reach blood (and target tissue) concentrations, which would be required to exert toxic effects on reproduction.

The possibility of a reduction in birth weights was raised by a recent study of a population in the Argentinean Andes that was exposed to high concentrations of boron in the drinking water (Igra et al. 2016). The preponderant industry in the study area was boron and lithium mining. It was reported that serum boron concentrations above 80 µg/L were inversely associated with birth length and weight. However, it remains open whether boron was in fact the causative agent in this case, because at the same time, also lithium exposure through the drinking water appeared associated with impaired foetal size (Harari et al. 2015). In addition, the high-altitude effect must be considered.

It follows that further investigations into reproductive effects of boron compounds are highly welcome. The authors should feel to be invited to submit relevant contributions on this matter to Archives of Toxicology.

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