



Effects of boron compounds on human reproduction

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Abstract

Because of the high pK_a of boric acid, inorganic borates, when taken up by the human or animal organism, exist in the body almost exclusively in the form of non-dissociated boric acid. Therefore, the variety of inorganic boron compounds is commonly addressed in the toxicological literature as “boron” (B). There is a discussion concerning categorisation of inorganic boron compounds as reproductive toxins. Boron treatment of rats, mice and dogs was dose-dependently associated with testicular toxicity, characterised by inhibited spermiation at lower dose levels and by reduction of epididymal sperm counts at higher dose levels. The NOAEL for such fertility effects of boric acid in male rats (oral feeding, Sprague Dawley strain) was evaluated to be 17.5 mg B/kg bw per day. As far as developmental toxicity is concerned, oral dosing of 9.6 mg B/kg bw daily to female pregnant Sprague Dawley rats remained without effects, with foetal skeletal effects observed at higher doses. Therefore, 9.6 mg B/kg bw (oral dosing) was evaluated as NOAEL for developmental effects of boric acid. The blood level in rats, equivalent to this NOAEL, is 1270 ng B/g. As far as B-exposed humans are concerned, field studies on the effect of boron on human reproduction are possible only in a few boron-rich geographical areas. Published field studies were conducted in China’s Liaoning province, the Argentinian Andes and Western Anatolia/Turkey. Particularly relevant are studies on occupationally B-exposed groups, because the potential exposure to boron is much higher in occupational compared to environmental settings. Comparison of estimated daily B exposure levels in humans and actually measured B blood levels confirms the preference of biomonitoring for exposure assessment in environmental and occupational studies. A boron blood level scaling shows that the levels of high occupational B exposures reported in China and in Turkey are compatible. Compared to the experimental B blood levels at boron-related NOAELs for male fertility and for developmental toxicity in rats, the human blood level means of the highest occupational exposure groups in China and in Turkey are lower by factors of >4 and >2 , respectively. Basically, concentrations of B within the body that exert reproductive toxicity in humans are not reached under the conditions of human normal handling and use, including conditions of extreme occupational exposures. In consequence, all relevant results of studies into human reproductive toxicity of B are basically negative. Considering the effective doses, there is no scientific contradiction between experimental and human results of B reproductive toxicity.

Keywords Boron · Boric acid · Borates · Reproductive toxicity · Fertility · Development

Introduction

There is a global interest in regulatory aspects of boron compounds, particularly in North America (Moore 1997; ATSDR 2010) Japan (Hasegawa et al. 2013) and Europe (ECHA 2010; SCCS 2010). A major focus of discussion is on reproductive toxicology (Duydu et al. 2016). For fertility and developmental toxicity, boric acid has been classified by the European Union as a “Category 1B” compound of the Globally Harmonized System (GHS), associated with risk phrases R60–61 (“may impair fertility; may cause harm to the unborn child”). Furthermore, boric acid has been

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proposed as a “substance of very high concern (SVHC)”, based on experimental studies.

By contrast, experimental studies also displayed beneficial effects of boron on reproductive functions. For instance, dietary boron supplementation (40 ppm) in male goats increased sperm output, sperm mobility and enhanced immune and antioxidant defence capacity (Krishnan et al. 2019), and a boron-deficient diet produced a negative impact on early embryonic development in rats (Lanoue et al. 1998). Inorganic boron compounds may counteract genotoxicity (Marat et al. 2018). Furthermore, evidence is accumulating that boron is nutritionally important (Nielsen 2000, 2008), an aspect of potential impact in animal health and production (Basoğlu et al. 2017; Abdelnour et al. 2018).

This complex situation has led to a dispute as to whether a categorisation of inorganic boron compounds as reproductive toxins is justified. The present review will highlight studies that contribute to this discussion.

Toxicokinetics of boric acid

Because of the high pK_a of boric acid, inorganic borates taken up by the human and animal organism exist almost exclusively in the form of non-dissociated boric acid. Therefore, the variety of inorganic boron compounds is toxicologically addressed as “boron”. The internationally preferred common dose measure is mg B, related to body weight.

The toxicokinetics of boric acid have been studied in animals and in humans (Jansen et al. 1984; Ku et al. 1991; Usuda et al. 1998; Murray 1998). Orally administered boric acid and borates are readily and completely absorbed and distributed and are renally excreted as boric acid. Because of the absence of metabolism elimination kinetics appear very similar for rodents and humans; minor species differences are owing to differences in glomerular filtration rates (Murray 1998).

As a result, there is a linear coherence between the boron dose/intake upon repetitive administration and boron levels in organs, including the testes. This was experimentally demonstrated in rats for a dose range up to 9000 ppm boric acid in the diet, equivalent to a dose of 68 mg B/kg bw per day (Ku et al. 1993).

Reproductive toxicity studies in animals

Fertility

Studies on the reproductive toxicity of boric acid pointed to testicular atrophy after high-dose boron treatment of male rodents. A Reproductive Assessment by Continuous Breeding (RACB) study using mice exposed to boric acid at 1000,

4500, and 9000 ppm in the diet indicated multiple sites of toxicity, with male fertility appearing as a sensitive endpoint. Decrements in sperm motility were observed at all exposure levels and testicular atrophy was confirmed in high- and middle-dose group males (Chapin and Ku 1994).

This was investigated further by timed serial sacrifice studies using 9000 ppm boric acid in the diet of rats, which found that the first lesion in the testis was an inhibition of spermiation (release of mature spermatids). With continued dosing, this was followed by a disorganisation of the normal ordered layering of the seminiferous epithelium, germ cell sloughing and death, and finally atrophy. Subsequent studies using additional boric acid doses (2000, 3000, 4500, 6000, and 9000 ppm) found that it was possible to observe inhibited spermiation that did not progress to atrophy (4500 ppm and below) within the 9-week exposure period. Also, once atrophic (from 9000 to 6000 ppm exposures), there was no return of spermatogenesis after refeeding of normal diet for 8, 16, 24, or 32 weeks, despite the presence of a normal-sized population of spermatogonia that was seen to divide. No effects were observed in rats treated with 2000 ppm. Testicular boron concentrations remained steady during exposure at the same level as found in blood and declined to background levels within 72 h after cessation of exposure. Bone boron levels were higher than in blood and maintained slightly elevated levels even 32 weeks after the cessation of exposure. These studies document the effects of boric acid on functional and structural aspects of the male reproductive system, demonstrating that the tissue concentration of boron, and not total dose, is important for the testicular toxicity and they indicate a threshold for these effects (Weir and Fisher 1972; Chapin and Ku 1994; Price et al. 1996).

In essence, boron treatment of rats, mice and dogs was dose-dependently associated with testicular toxicity, characterised by inhibited spermiation at lower dose levels, and by reduction of epididymal sperm counts at higher dose levels (Weir and Fisher 1972; Fail et al. 1991; Ku et al. 1993). The NOAEL for fertility effects of boric acid in male rats (oral feeding, Sprague Dawley strain) was evaluated to be 17.5 mg B/kg bw per day [evaluation of ECHA (2010), based on the data of Weir and Fisher (1972)].

Developmental toxicity

The developmental toxicity of boric acid (given orally) was investigated in rats, rabbits and mice, within the framework of the US National Toxicology Program (Heindel et al. 1992, 1994). Boric acid was provided in the feed to mice and rats at 0, 0.1, 0.2, or 0.4% throughout gestation. Average doses (mg/kg/day) were 248, 452, or 1003 for mice, and 78, 163, or 330 in rats. A separate group of rats received 0.8% boric acid in the feed or 539 mg/kg/day only on gestation days 6–15. Rabbits were given boric acid (0, 62.5, 125,

or 250 mg/kg) by gavage on gestation days 6–19. Maternal body weight, food and/or water consumption and signs of toxicity were monitored at regular intervals. At termination, on gestation days 17 (mice), 20 (rats), or 30 (rabbits), the uterus was examined to determine the number of resorptions, dead or live fetuses. Mouse dams exhibited mild renal lesions (at 248 mg/kg/day boric acid and above), increased water intake and relative kidney weight (1003 mg/kg/day boric acid), and decreased weight gain during treatment. Maternal rats exhibited increased liver and kidney weights at 2163 mg/kg/day boric acid, altered water and/or food intake at > 163 mg/kg/day boric acid, and decreased weight gain at > 330 mg/kg/day boric acid. In rabbits, signs of toxicity included decreased food consumption during treatment and vaginal bleeding associated with pregnancy loss at 250 mg/kg/day. Maternal body weight (gestational days 9–30), weight gain during treatment, and gravid uterine weight decreased at 250 mg/kg/day. Relative maternal kidney weight (but not absolute weight) was increased at 250 mg/kg/day, but microscopic evaluation did not indicate any renal pathology associated with exposure. It was concluded that boric acid is a developmental toxicant in all three species. The lowest-observed-adverse-effect level (LOAEL) for developmental toxicity was 78 mg/kg/day for rats (foetal weight reduction), 250 mg/kg/day for rabbits (prenatal mortality and malformations), and 452 mg/kg/day for mice (foetal weight reduction). The no-observed-adverse-effect levels (NOAELs) for developmental toxicity in these species were < 78 mg/kg/day (rats), 125 mg/kg/day (rabbits), and 248 mg/kg/day (mice). With regard to maternal toxicity, the rat was the most sensitive (163 mg/kg/day), while both the mouse and rabbit showed maternal toxicity at 250 mg/kg/day. Thus, developmental toxicity occurred below maternally toxic levels in the rat and in the presence of maternal toxicity in mice or rabbits.

Related to elementary boron, decreased foetal weights were noted in the above-mentioned study of the US National Toxicology Program at 13.7 mg B/kg bw per day in absence of maternal toxicity (Heindel et al. 1992). In a subsequent study (Price et al. 1996), oral dosing of 9.6 mg B/kg bw daily to pregnant Sprague Dawley rats remained without effects, with foetal skeletal effects observed at higher doses. Thus, 9.6 mg B/kg bw (oral dosing) was evaluated as NOAEL for developmental effects of boric acid (WHO 1998; ECHA 2010; WHO 2011).

Combination of toxicokinetic and reproductive toxicity data

Subsequent to their studies of developmental toxicity, Price et al. (1997) studied the blood levels reached under the experimental conditions of the preceding study. For this reason, timed-mated Sprague Dawley rats (28–32/group) were

exposed to boric acid in the diet from gestational days 0–20. Dietary concentrations of added boric acid were identical to those of the preceding developmental toxicity study and yielded average daily intakes of 0, 3, 6, 10, 13, or 25 mg boron/kg body weight (rounded values). Increasing dietary concentrations of boric acid were correlated with the whole blood boron concentrations in confirmed pregnant rats, amounting to 0.229 ± 0.143 , 0.564 ± 0.211 , 0.975 ± 0.261 , 1.27 ± 0.298 , 1.53 ± 0.546 , and 2.82 ± 0.987 $\mu\text{g B/g}$ blood (mean \pm SD), from the control through high-dose groups. Maternal blood boron concentrations correlated with indices of maternal dietary intake of boron and with embryo/foetal toxicity that was observed at the two upper dose levels. The authors concluded that blood boron concentrations of 1.27 ± 0.298 and 1.53 ± 0.546 $\mu\text{g B/g}$ blood were associated with the NOAEL (rounded to 10 mg B/kg/d) and LOAEL (rounded to 13 mg B/kg/d) for developmental toxicity, respectively (Price et al. 1997). Thus, the accepted NOAEL for rat developmental toxicity is equivalent to a blood level in rats of 1270 ng B/g.

The plausibility of these data can be checked against the independent data set of Ku et al. (1991), who performed a tissue distribution study in male Fischer rats at a daily oral dose of 9000 ppm boric acid in the diet, i.e. 4.5-fold higher than the highest dose level of Price et al. (1996, 1997). From the 2nd day of treatment on, the plasma levels ranged between 14.03 and 16.37 $\mu\text{g B/ml}$. Assuming an equal distribution of B between blood plasma and blood cells (which is supported by an almost equal distribution in most tissues), this is about 5.3-fold higher compared to the highest dose level of Price et al. (1997). Considering the different rat strains used and remaining uncertainties in the whole blood/plasma distribution, both data sets appear compatible. This also implies no major sex differences. Hence, upon extrapolation of the data of Price et al. (1997), the commonly accepted NOAEL for rat male reproductive toxicity is equivalent to a blood level of about 2300 ng B/g.

Reproductive toxicity studies in humans

Field studies on the effect of boron on human reproduction are possible only in boron-rich geographical areas. Such areas are (semi)arid, with a history of geothermal activity. Published studies were conducted in China's Liaoning province, the Argentinian Andes and Western Anatolia/Turkey. Particularly relevant are studies on occupationally B-exposed groups, because the potential exposure to boron is much higher in occupational compared to environmental cohorts.

Studies in China

Owing to the geological situation, high boron exposures are reported in parts of Northeast China, and are related to environmental, lifestyle and occupational factors (Chang et al. 2006).

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. Employed men living in the same community and in a remote community were used as controls. Boron workers ($n=75$) had a mean daily boron intake of 31.3 mg B/day, and a subset of 16 of these men, employed at a plant where there was heavy boron contamination of the water supply, had an estimated mean daily boron intake of 125 mg B/day. Estimates of mean daily boron intake in local community and remote background controls were 4.25 mg B/day and 1.40 mg B/day, respectively. Reproductive outcomes in the wives of 945 boron workers were not significantly different from outcomes in the wives of 249 background control men after adjustment for potential confounders. There were no statistically significant differences in semen characteristics between exposure groups, including in the highly exposed subset, except that sperm Y:X ratio was reduced in boron workers. Within exposure groups, the Y:X ratio did not correlate with the boron concentration in blood, semen and urine. 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).

Studies in Argentina

The possibility of a reduction of birth weights related to boron was raised by a study of a population in the Argentinean Andes. This population was exposed to elevated concentrations of boron in the drinking water (Igra et al. 2016). The predominant industry in the study area was boron and lithium mining. It was reported that serum boron concentrations above 80 $\mu\text{g/L}$ were inversely associated with length and weight of newborns. [All other studies give B concentrations per gram of whole blood.] However, it remains open whether boron was the causative agent in this case, because in the same population and at the same time also lithium exposure through drinking water was associated with impaired foetal size (Harari et al. 2015). Also, high altitude, which has a profound

impact on birth weight (Jensen et al. 1997) may have confounded the data. Hence, no firm conclusions can be drawn from these studies.

Studies in Turkey

A first series of studies into human reproductive toxicity has been performed in environmentally exposed populations residing in boron-rich areas of Turkey with high drinking water levels and no clear-cut effects on reproduction were observed (Şaylı et al. 1998; Korkmaz et al. 2007). Also, fertility figures (Şaylı 1998; Şaylı et al. 1998; Korkmaz et al. 2011) and spontaneous abortions and stillbirths (Tüccar et al. 1998) showed no difference between subpopulations with high vs. low boron exposure.

To get an insight into the possible level of environmental exposure, Korkmaz et al. (2011) estimated daily B exposure in 66 males in Turkey living in a B-rich area. The average daily B exposure value was calculated as 6.77 mg B in the study group as opposed to 1.26 mg B in control areas.

In an occupational setting within a boric acid/borate production zone at Bandırma/Turkey Duydu et al. (2011) studied male persons exposed to boron both occupationally and via drinking water. The study investigated possible reproductive effects of boron exposure in workers employed in a boric acid production plant. Boron was analysed in biological samples (blood, urine, semen), in workplace air, in food, and in water sources. Unfavourable effects of boron exposure on the reproductive toxicity indicators (concentration, motility, morphology of the sperm cells and blood levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone) were not observed. The mean calculated daily boron exposure (DBE) of the highly exposed subgroup was 14.45 ± 6.57 (range: 3.32–35.62) mg/day.

An extension of this study investigated the relation between DNA-strand breaks (COMET assay, neutral and alkaline version) in sperm cells and sperm quality parameters. A correlation between blood boron levels and mean DNA-strand breaks in sperm was weak and DNA-strand breaks in sperm were statistically not different between control and exposed groups. It was concluded that boron exposures had no dose-dependent contribution in addition to already pre-existing DNA-strand breaks in the sperm cells. Weak but statistically significant correlations between DNA-strand breaks and motility/morphology parameters of sperm samples were observed in the neutral version of the COMET assay, while correlations between the same variables were statistically not significant in the alkaline version (Duydu et al. 2012).

In another independent study, (Duydu et al. 2018a) investigated possible boron-associated effects on male reproduction in workers ($n=212$) under different boron exposure conditions in the boron mining area of Bigadic. The mean

daily boron exposure (DBE) and blood boron concentration of workers in the “extreme” exposure group ($n=98$) were 47.17 ± 7.47 (range: 7.95–106.8) mg B/day and 570.6 ± 160.1 (range: 402.6–1100) ng B/g blood, respectively. Boron-associated adverse effects on semen parameters, as well as on FSH, LH and total testosterone levels were not seen, even within the “extreme” exposure group.

Hundred and ninety-nine females residing in Bandırma and Bigadic participated in a study investigating pregnancy outcomes. The study group covered boron blood levels from low (< 100 ng B/g blood, $n=143$) to high (> 150 ng B/g blood, $n=27$) concentrations. The mean blood boron concentration and the mean estimated daily boron exposure of the high exposure group was 274.58 (range: 151.81–975.66) ng B/g blood and 24.67 (range: 10.47–57.86) mg B/day, respectively. In spite of the high levels of exposure, boron-mediated adverse effects on induced abortion, spontaneous abortion (miscarriage), stillbirth, infant death, neonatal death, early neonatal death, preterm birth, congenital anomalies, sex ratio and birth weight of newborns were not observed (Duydu et al. 2018a, b). This negative outcome was supported by additional studies of possible DNA damage in the lymphocytes and buccal cells of females, assessed by Comet and micronucleus assays. No significant difference was observed in the DNA damage of the lymphocytes of B-exposed groups of female volunteers in Comet assay. Buccal micronucleus frequency observed in the high exposure group was even significantly lower than the low exposure group ($p < 0.05$) (Başaran et al. 2019a).

Boron-associated shifts in sex ratios at birth (based on decrease in Y- vs. X-bearing sperm cells) had been suggested based in studies in China (*v.s.*). Therefore, a new independent study on this particular topic was started and 304 male workers in Bandırma and Bigadic (Turkey) with different degrees of occupational and environmental exposure to boron were investigated (Duydu et al. 2019). Boron was quantitated in blood, urine and semen and the persons were allocated to exposure groups along B blood levels. In the highest (“extreme”) exposure group ($n=69$), calculated mean daily boron exposures, semen boron and blood boron concentrations were 44.9 [range 7.95–196] mg B/day, 1643 [range 188–1886] ng B/g semen and 554 [range 402–2000] ng B/g blood, respectively. Overall, an association between boron exposure and Y:X sperm ratios in semen was not statistically significant ($p > 0.05$). Also, the mean Y:X sperm ratios in semen samples of workers allocated to the different exposure groups were statistically not different in pairwise comparisons ($p > 0.05$). Additionally, a boron-associated shift in sex ratio at birth towards female offspring was not visible. These results did not support an association between boron exposure and decreased Y:X sperm ratio in males, even under extreme boron exposure conditions (Duydu et al. 2019).

This study was supplemented by an extension on 102 male workers who were occupationally exposed to boron from Bandırma and 110 workers who were occupationally and environmentally exposed to boron from Bigadic. DNA damage in the sperm, blood and buccal cells of 212 males was evaluated by Comet and micronucleus assays. No significant increase in the DNA damage in blood, sperm and buccal cells was observed in persons exposed to boron both occupationally and environmentally (Başaran et al. 2019b).

Discussion and conclusion

Experimentally, inorganic boron compounds (boric acid and borates) may exert toxic effects on reproduction. For these effects, a NOAEL (no-observed-adverse-effect-level) of 17.5 mg B/kg-bw/day has been identified by official bodies for the (male) reproductive effects of boron in a multigeneration study of rats (as the most susceptible species) and a NOAEL for the developmental effects in rats was identified at 9.6 mg B/kg-bw/day (WHO 1998; ECHA 2010; WHO 2011).

By contrast, neither boron-related male reproductive nor developmental effects have been ascertained in human populations exposed to high B levels.

The exposure data of studies as discussed above are compiled in Table 1. The following conclusions can be drawn from this compilation:

- A comparison of estimated daily B exposure levels and measured B blood levels confirms the preference of bio-monitoring data for a comparison of human field studies. This relates to both environmental and occupational field studies.
- The B blood level scaling clearly shows that high occupational B exposures reported in China and in Turkey are almost compatible.
- Compared to the B blood levels at the boron-related NOAELs for male fertility and for developmental toxicity in rats, the blood level means of the highest occupational exposure groups in China and in Turkey are lower by factors of > 4 and > 2 , respectively. Part of the persons in the highest B exposure groups in China and in Turkey reach or exceed the experimental B blood levels at the NOAEL for developmental toxicity in rats. Part of the persons in the highest B exposure group in China reach or exceed the experimental B blood levels at the NOAEL for an impairment of (male) fertility in rats.

This demonstrates that there is no basic contradiction between the human and experimental reproductive toxicity data for boric acid/borates, as effect levels are definitely

Table 1 Synopsis of human and experimental exposures to boric acid/borates and associated boron blood levels (means or median and range; values rounded to 2 digits); ranking of human studies according to exposure levels. Adopted from Bolt et al. (2012), updated and modified

	Estimated daily B exposures	B blood levels (whole blood)
Human studies	mg per day	ng B/g blood
Turkey, env. (Şaylı et al. (1998; Korkmaz et al. 2007) (high dose "Group I")	6.8 [1.8–23]	–
Argentina, env. (Igra et al. 2016) (total cohort of mothers)	–	130* [0.73–610]*
Turkey, env. + occup. (Tüccar et al. 1998) (high exposure group)	14.5 [3.3–36]	220 [150–450]
Turkey, env., females (Duydu et al. 2018b) (high exposure group)	25 [10–58]	280 [152–980]
USA, occup. (Culver et al. 1994) ("high dust exposure group")	28 –	260 [up to 330]
China, occup. (Scially et al. 2010; Robbins et al. 2010) (high exposure group)	37 [2.3–470]	500 [20–3600]
Turkey, occup., males (Duydu et al. 2019) ("extreme" exposure)	45 [8.0–200]	550 [400–2000]
Experimental studies	mg/kg per day	ng B/g blood
Rat NOAEL, fertility (Weir et al. 1972)	18	2300
Rat NOAEL, devel. tox. (Price et al. 1996)	9.6	1300

Occup. occupational, env. environmental B exposure

*Assuming equal distribution of B between serum and blood cells (v.s., "Toxicokinetics of boric acid")

higher compared to NOAELs. Human B exposures, even in the highest exposed cohorts, are too low to reach the blood (and target tissue) concentrations, which would be required to exert toxic effects on reproduction. In this context, it must be noted that the highest exposures reported in China and in Turkey truly represent the worst-case human exposure conditions that are feasible today. Therefore, concentrations of B within the body that exert reproductive toxicity in humans are not be reached under the conditions of human normal handling and use, including conditions of most extreme occupational exposures. Therefore, all relevant human study results are negative.

The question remains how this scientific situation is translated into the regulatory context. Chapter 3.7.2.3.1 of the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) says: "Classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence. This means that all available information that bears on the determination of reproductive toxicity is considered together. Included is information such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs"... In addition, chapter 3.7.2.3.2 says: "Toxicokinetic studies in animals and humans, site of action and mechanism or mode of action study results may

provide relevant information, which could reduce or increase concerns about the hazard to human health"...

In essence, the present categorization of inorganic boron compounds (boric acid and borates) should be reconsidered.

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