Regulatory Toxicology and Pharmacology 121 (2021) 104873

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Comprehensive Review

Toxicity of boric acid, borax and other boron containing compounds: A review

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ARTICLE INFO

Handling editor: Dr. Lesa Aylward

Keywords:
Inhalation
Oral
Dermal
Comet assay
Micronucleus
Micronuclei
Chromosomal aberrations
Mutation

ABSTRACT

Boron, often in the form of boric acid, is widely used as a flame retardant in insulation products, and although humans ingest boron through food, high exposure may lead to unwanted health effects. We assessed the toxicity of boric acid, borax and other forms of boron, after inhalation, dermal and oral exposure. After oral exposure, boron is absorbed over the gastrointestinal tract. Intact skin seems to pose a more effective barrier to boron than compromised skin. Boron excretion seems to mainly occur via the urine, although after skin exposure boron has been demonstrated in bile and gastrointestinal contents. Inhalation toxicity data are sparse, but one animal study showed reduced foetal weight after inhalation of cellulose that had a boric acid content of 20%. Skin exposure to boric acid has proven fatal in some cases, and the range of toxicity effects include abdominal as well as local effects on the skin. Fatalities from boric acid also have occurred after oral ingestion, and the endpoints in animals are weight loss and reproductive toxicity. Concerning genotoxicity studies, the overall picture indicates that boron-containing compounds are not genotoxic. There was no evidence of the carcinogenicity of boric acid in a 2-year study in mice.

1. Introduction

Boron is found in plants and drinking water, and may be an essential trace element in humans (Murray, 1998; Richold, 1998). Borates—salts of boric acid (H_3BO_3) —are used in laundry detergents, cleaning agents and fertilisers. Boron has historically been used as an ingredient in pharmaceuticals (Burgos et al., 2018; Gupta and Daigle, 2014; Paton, 2017; Soriano-Ursúa et al., 2019), and in fluorescent sensors for biological research (Pagano and Chen, 1998). From approximately 1870 and 50 years on, boric acid and borax (sodium tetraborate decahydrate, $Na_2B_4O_7$ $10H_2O$) were used as food preservatives (e.g., prevented food spoilage during WWI) (Richold, 1998). Boron nitride (BN) is a constituent of some spray-formulated greasing agents (3M_Technical_-Ceramics, 2020), and boric acid, borax, and other boron-containing compounds are commonly used as flame-retardants in insulation materials (e.g., in cellulose products) (Pleus et al., 2018).

During handling of boron nitride-containing sprays, boron-impregnated insulation products or fertilisers, worker exposure potentially occurs through the dermal and inhalation pathways. Therefore, it is important to determine at what exposure levels boron becomes toxic. To address this, we reviewed the toxicological literature concerning inhalation and dermal exposure. In addition, we reviewed the literature regarding its oral exposure, because these studies contribute to the understanding of the toxicity endpoints potentially elicited by the two aforementioned pathways. We also reviewed the genotoxic and carcinogenic potential of boron compounds, and we did this for all exposure pathways as well as for *in vitro* studies. The inclusion of the latter group of experiments is justified by the notion that genotoxic events including mutagenicity in general occur inside cells. As a reference to prior work we note that the reproductive toxicity of boron compounds was recently reviewed in (Bolt et al., 2020); and the European Food Safety Authority in 2013 evaluated boric acid and borax as food additives (EFSA, 2013).

To compile this literature review, we retrieved relevant articles from the PubMed database (Pubmed, 2020) by using combinations of the search terms: “boron”, “boric acid”, “toxicity”, “inhalation”, “oral”, “dermal”, “skin”, “genotoxicity”, and “carcinogenicity”. We supplemented this search strategy with the reading of reference lists of the retrieved articles to identify additional literature with an older date. We determined that a total of 106 articles were relevant for inclusion in the current article.

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https://doi.org/10.1016/j.yrtph.2021.104873
Received 23 June 2020; Received in revised form 6 January 2021; Accepted 18 January 2021
Available online 22 January 2021

2. Normal levels of boron

We present normal bodily fluid and tissue levels reported in a number of studies in Fig. 1. Studies on normal levels in humans have a mean boron level in blood of 241 μg B/L and in urine of 1130 μg B/L; and, different concentrations in tissues range from 0.06 to 1.2 mg B/kg.

3. Inhalation toxicity

When we assess occupational exposure, both the inhalation and skin toxicity pathways may be in play simultaneously. Nonetheless, we present the occupational exposure studies in this inhalation toxicity section. Some epidemiological studies have addressed whether boric acid causes reproductive toxicity. One Chinese study investigated the semen quality of 75 workers exposed to a mean level of 31 mg boron per day; 16 of them even had an estimated exposure of 125 mg B/day (1.8 mg B/kg bw). The exposure in the local community was 4.3 mg B/day, whereas the background level was 1.4 mg B/day. The only semen characteristic affected in the workers was a decreased Y:X chromosome ratio—but the ratio did not correlate with boron levels in the blood (Robbins et al., 2008; Scialli et al., 2010).

Other studies of reproductive endpoints showed no effects. Workers who were exposed to boron had a mean blood level of 499 μg B/kg, whereas workers with no known exposure to boron and residing either in a) an area with boron industries, or b) an area with only low amounts of boron in soil and groundwater, had blood concentrations of 96 and 48 μg B/kg, respectively. Boron concentrations did not correlate with sperm endpoints: concentration, motility, or morphology (Robbins et al., 2010). Likewise, no reproductive effects were observed in 204 workers who worked at a boric acid production plant located in Bandırma, Turkey. The mean blood concentration of boron was 224 μg/kg in a high-exposure group; this level is within the normal range depicted in Fig. 1 (Başaran et al., 2012). Moreover, no reproductive endpoint effects were observed in another study of workers from the same location (Duydu et al., 2011). A group of 304 male workers in Bandırma and Bigadic, Turkey were investigated. They had varying occupational and environmental boron exposure. No association was seen between boron exposure and Y:X sperm ratios, nor was there any shift in sex ratio at birth towards female offspring (Duydu et al., 2019).

Concerning non-reproduction endpoints, 113 workers who were exposed to boron oxide and boric acid dusts at on average of 4.1 mg particulate dust/m^3 were interviewed. In comparison to 214 controls, they reported more symptoms of eye irritation; dryness of the nose, mouth, or throat; sore throat; and productive cough (Garabrant et al., 1984).

An OECD 414 Prenatal Developmental Toxicity study in rats was conducted with cellulose insulation containing 20% boric acid (3.5% B). The inhalation levels were 15, 90, and 270 mg/m^3. Toxicity was only observed at the two highest doses: the pregnant rats had increased incidence of what was described as “gross lesion in lung or liver”, and their lungs were pale. The pups had a 7% reduction in foetal body weight, but no embryo/foetal developmental endpoints were affected. If one considers a 7% reduction in body weight to be adverse, the dose descriptors are: No-Observed-Adverse-Effect Concentration (NOAEC)-$_{material}$: 15 mg/m^3; $NOAEC_{boric\ acid\ content}$: 3 mg/$m^3$, and $NOEAC_{B\ content}$: 0.53 mg/m^3. Notably, it cannot be excluded that the toxicological effects were mediated by the cellulose fibres rather than the boron content (Pleus et al., 2018).

4. Dermal toxicity

4.1. Absorption and excretion of boron after dermal application of boric acid or borax

Concerning intact skin, human volunteers had either boric acid or borax applied. The absorption values were approximately 0.2% of the dose, and the flux values were 0.009 μg/cm^2 (Wester et al., 1998). Boric acid formulated in water-based jelly caused increased levels of boron in blood and urine levels of infants (Stüttgen et al., 1981). In 22 newborns, there was no increase in the plasma level of boron after the daily topical application of a boric acid ointment in the area covered by the napkin (Friis-Hansen et al., 1982).

Concerning compromised skin, transcutaneous absorption was observed in one 7-month-old infant who died after being treated for eczema with boric acid. The compound was found in bile and in gastrointestinal tract contents (Kaufmann et al., 1962). In contrast, boric acid present in talc was found not to be absorbed in infants when applied to areas with erythema (Vignec, 1954). A number of animal studies suggest that compromised skin is a poorer barrier than intact skin. The intact skin of rabbits was applied with various formulations of boric acid: boric acid in 5% solution, boric acid crystals, borated powder, boric acid in talc, boric acid in ointment, or boroglycerine. There was very little excretion of boric acid in the urine—between 0.4 and 4.6 mg/kg bw[1] per 24 h. When skin was abraded, the excreted amounts of boron were higher—between 1.4 and 7.6 mg/kg bw per 24 h; and when the skin was burnt and partially denuded, the amount of excreted boric acid increased to between 10 and 125 mg/kg bw per 24 h (Draize and Kelley, 1959). Rats were applied with three different formulations of boric acid—two oleaginous ointments and one aqueous jelly. After application to intact skin, there was only a minor increase in boric acid urine levels. In contrast, when applied to damaged skin, the urine concentration of boric acid was 4- to 8-fold higher than controls after application of the ointments and 34 times higher than controls after the jelly (Nielsen, 1970).

Concerning excretion, boron was increased in urine after dermal application in rabbits (Draize and Kelley, 1959) and in rats (Nielsen, 1970, 2009).

4.2. Fatalities after human skin exposure

A 4-month-old girl was treated for dermatitis (“diaper rash”) for 1 week with boric acid ointment; but, as this did not relieve the symptoms, she was further bathed in a boric acid solution and had her skin intermittently dusted with boric acid crystals. These latter treatments were done over the next 2 weeks. The rash worsened, and the treatment with boric acid was discontinued; the infant began having loose stools, and a sore throat was treated with Argyrols (silver) and Vicks ointment (containing several ingredients). The child developed difficulty breathing and was hospitalised. A range of signs and symptoms ensued, and eventually the infant died. The blood level of boric acid was 22 mg/L (3.9 mg B/L). The cerebrospinal fluid contained 50 mg boric acid/L (8.8 mg B/L). The tissue levels of boric acid were 36.8 mg B/kg (kidney), 17.5 mg B/kg (liver), 2.1 mg B/kg (brain), and 1.9 mg B/kg (muscle)—levels considerably higher than the normal human levels presented in Fig. 1. The 4-month-old twin brother of the former case was also hospitalised due to the same treatment regimen. The symptoms included diarrhoea, vomiting and dehydration; his blood level of boric acid was 18.8 mg/L (3.3 mg B/L) and the urine level was 30 mg/L (5.3 mg B/L). He eventually recovered (Ducey and Williams, 1953). A 35-year-old woman who had varicose veins for a number of years treated a generalised rash for 14 days with wet dressings saturated with boric acid solution. Some 11 days into the regimen, she became lethargic and subsequently comatose; she later died. Her boric acid levels were as follows: 138 mg B/kg (liver), 121 mg B/kg (brain), 166 mg B/kg (spinal fluid), 919 mg B/kg (urine) and 613 mg B/kg (blood). These values are

[1] In this older study, it is not specified what the kg in “mg/kg” pertains to. We find it likely that this is per kg body weight (bw), as it is reported in the article that in “animals with partially denuded skin absorbed sufficient quantities of boric acid to excrete up to 345 mg (126.9 mg/kg) of boric acid in a 24-h period.” This corresponds to a body weight in rabbits of 3 kg.

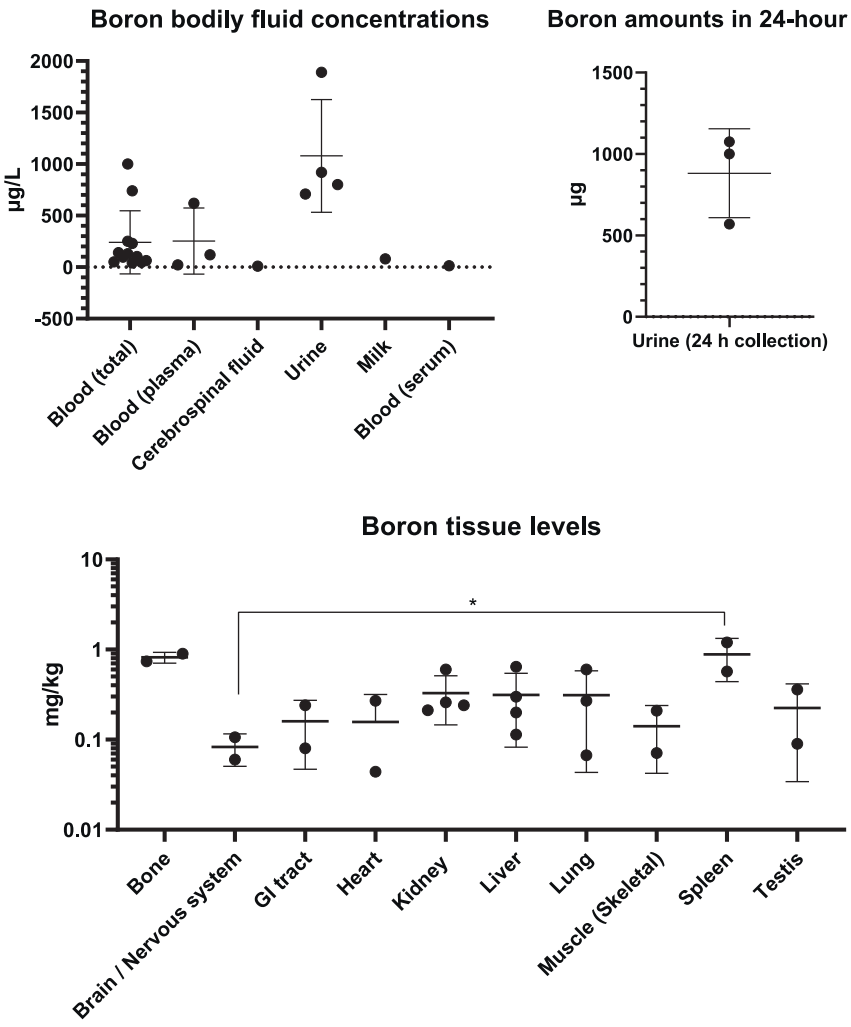

Fig. 1. Normal levels of boron in bodily fluids and tissues of humans. The values were obtained from a comprehensive review by (Lyengar et al., 1978), and supplemented for bodily fluids with (Forbes et al., 1954; Friis-Hansen et al., 1982; Minoia et al., 1990; Pahl, 2001; Robbins et al., 2010; Stüttgen et al., 1981; Vignec, 1954), and for the nervous system (Forbes et al., 1954). For tissue levels, only tissues for which there were at least two samples were included. The single data points represent mean values of independent studies. The mean value of all studies is designated with a horizontal line, and the bar designates standard deviation (SD). * designates a *p*-value of less than 0.05 in the one-way analysis of variance (ANOVA) post-test: the Tukey multiple comparisons test.

considerably higher than the normal levels presented in Fig. 1 (Jordan and Crissey, 1957). A 7-month-old infant died after being treated for eczema for several days with dressings containing 3% boric acid. The level of boric acid in bodily fluids and tissues were as follows: 44 mg B/kg serum, 35 mg B/kg bile, 32 mg B/kg gastrointestinal tract contents, 21 mg B/kg brain, 18 mg B/kg kidney, 22 mg B/kg liver, and 32 mg B/kg spleen (Kaufmann et al., 1962). A 9-month-old girl was admitted to the hospital after having been treated for dermatitis (diaper rash) with boric acid. She had erythema and excoriation of the skin; she had become lethargic and semicomatose, with vomiting and high fever. A number of additional symptoms were observed after hospitalisation, including dehydration, cyanosis, and convulsions. She became comatose, and died 26 h after hospitalisation. Her boron tissue levels were 210 mg B/kg in whole blood, 200 in serum, 240 in brain, 290 in liver, 280 in kidney, 220 in heart, 370 in thymus, 340 in muscle, and 30 in adipose tissue (Brooke and Boogs, 1951).

4.3. Dermal toxicity without fatal outcome

A 27-day-old girl had dermatitis, for which she was treated with boric acid powder sprinkled onto the area normally covered by the diaper. This treatment was done 15 to 20 times over a 48-h period. At hospitalisation, she had for the previous 24 h had fever, vomiting, diarrhoea, and irritability. After 10 and 34 h of dialysis, the boric acid serum levels were 303 and 154 mg/L (equal to 53 and 27 mg B/L). She recovered and had no persistent symptoms at a 2-month follow-up investigation (Baliah et al., 1969). Goldbloom and Goldbloom reported four cases of boric acid poisoning in infants, with symptoms of erythematous skin eruptions, diarrhoea, and vomiting. In addition, a fifth case, a 27-day-old infant, presented with vomiting, convulsions, erythema and desquamation of the face and abdomen (Goldbloom and Goldbloom, 1953). One male infant aged 27 days who had been treated for dermatitis with borated talc followed by boric acid powder for 7 days was hospitalised with gastroenteritis after having vomited all feedings for 3 days. His symptoms also included erythematous patches on several body parts, and subsequent excoriation of the skin. The blood and urinary levels of boric acid were 8.8 mg B/L and 49 mg B/L, respectively (Ducey and Williams, 1953).

5. Oral exposure

5.1. Absorption and excretion

The uptake of boric acid was investigated in six individuals. Two preparations were tested, one water solution and one water emulsifying ointment. The 96-h urinary excretion was 94% and 92%, respectively, indicating an almost complete absorption, and suggesting that the urinary excretion pathway is prominent in boron excretion (Aas Jansen et al., 1984). A man, 82 years of age, ingested a large amount of boric acid, and 3 h later had a serum level of 315 mg B/L (Corradi et al., 2010). In one infant who in an accidental poisoning through a stomach tube was given 2 g boric acid (130 mg B/kg bw), the urinary excretion was followed over 23 days. The urinary concentration of borate decreased from approximately 25 mg B/L to approximately 7 mg B/L 5 days later,

and over the next 18 days to approximately 2 mg B/L (Wong et al., 1964).

Pregnant rats were administered boric acid at 5, 10, or 20 mg B/kg bw/day by oral gavage on gestation days 6–21. The offspring were dosed the same levels on postnatal days 1–28. Boron was dose dependently increased in plasm from the pups from approximately 0.1 μg/L in controls to 11 μg/L at the highest dose (Watson et al., 2020). Rats were administered boric acid via their feed (at 9000 mg/kg = ~189 mg B/kg bw/day[2]) for up to 7 days. Boron was increased in plasma, liver, kidney, brain, intestine, testes muscle and bone (Ku et al., 1991). Boron-containing acids have in an intraperitoneal injection study been demonstrated to enter the central nervous system (Soriano-Ursúa et al., 2014). Boron, dosed as tetraborate ($Na_2B_4O_7$) to rats, was rapidly absorbed and excretion was demonstrated through urine mediated by glomerular filtration (Usuda et al., 1998).

5.2. Acute toxicity case studies with fatalities after ingestion of boric acid

Wong et al. described an accidental poisoning in which 5 of 11 infants died after ingesting infant formulae prepared from a bottle of "distilled" water that accidently contained 2.5% boric acid. The amounts of ingested borate was between 2 and 14 g—with a mean level in those who died of 8.5 g borate (1.5 g B = 500 mg B/kg bw), and in those who survived approximately 170 mg B/kg bw. The symptoms included central nervous system irritation; vomiting and diarrhoea; as well as erythema, exfoliation, and desquamation of the skin (Wong et al., 1964). A man aged 77 years had ingested approximately 30 g of boric acid (~76 mg B/kg bw). He developed vomiting and diarrhoea, and acute renal failure was suspected. He died from cardiac insufficiency (Ishii et al., 1993). One man aged 45 years ingested approximately two cups of boric acid crystals in a suicide attempt. He shortly thereafter experienced nausea, vomiting, diarrhoea, and dehydration. After 2 days, he was hospitalised with generalised erythematous rash, hypotension, renal failure, and metabolic acidosis. He developed cardiac symptoms and died. Fifty-two hours after ingestion his blood level of boric acid was 74 mg B/L and the urine level was 280 mg B/L (Restuccio et al., 1992). An 18-month-old girl died after accidently ingesting a pesticide that contained boric acid. The post-mortem examination showed cerebral oedema and pulmonary congestion and oedema. The concentration of borate in her heart blood was 14.6 mg B/L, and the concentration in the gastric contents was 1060 mg B/L (Hamilton and Wolf, 2007). A male infant 5 days of age had ingested 6–9 g boric acid (~300–500 mg B/kg bw). He was irritable, hyperactive, and had erythema. Subsequently, vomiting, central nervous system depression and desquamation of the skin ensued; he became anuric and died (Segar, 1960).

5.3. Acute toxicity cases with no fatalities after ingestion of boric acid

Two infants were hospitalised after having ingested boric acid: one 3 month-old had ingested 115 mg B/kg bw. His symptoms included dehydration, tachypnoea, tachycardia and oliguria. In a 40-day-old girl, the intake was approximately 450 mg B/kg bw, and her symptoms included acidosis, tachycardia and elevated blood pressure (Pedicelli et al., 2015). Siblings 24 days and 14 months of age accidently ingested a boric acid solution at 93 mg B/kg bw and 31 mg B/kg bw, respectively. The peak boric acid concentrations in serum were 25.7 mg B/L in the youngest child and 9.8 mg B/L in the other. Erythema was seen on both children, and the youngest was irritable, was vomiting, and had mild diarrhoea. At a follow-up, 1 month later, both children were asymptomatic (Baker and Bogema, 1986). A man aged 62 years who was undergoing an oral glucose test was accidently given boric acid (~100 mg B/kg bw). He was treated by dialysis, but experienced metabolic acidosis, total anuria lasting 14 h and anaemia (Stolpmann and Hopmann, 1975). A 26-year-old woman was hospitalised after having attempted suicide by ingesting boric acid (~50 mg B/kg bw). She had impaired consciousness, vomiting, fever, shivering, and skin flush. Before treatment was started, she had a serum concentration of 465 mg boric acid/L (81 mg B/L) and a urinary concentration of 3400 mg/L (595 mg B/L). The biological elimination half-life in serum was 13.5 h (Teshima et al., 1992).

In some cases, the exact amount of boric acid ingested was unknown; the symptoms included erythema and desquamation (Schillinger et al., 1982); lethargy, stiffness and erythema (Webb et al., 2013); vomiting, lethargy and erythema (Segar, 1960); and vomiting, rapid pulse, irregular respiration and erythema (Connelly et al., 1958). Litowitz et al. reviewed 784 cases of boric acid ingestion recorded at two poison centres. Except for two cases, all were acute intoxications. The most frequent symptoms were abdominal pain, vomiting, and diarrhoea. Less frequent ones were headache, light-headedness, lethargy, and rash (Litovitz et al., 1988). Linden et al. described 364 cases of boric acid exposure reported to a poisoning centre. Of these, one case was fatal. The common symptoms included vomiting, nausea, diarrhoea, and abdominal cramps (Linden et al., 1986). Notably, a number of boron-containing pharmaceuticals have passed safety testing and are presently used in humans (Burgos et al., 2018; Gupta and Daigle, 2014; Paton, 2017; Soriano-Ursúa et al., 2019).

5.4. Data from animal studies on the toxicity of boric acid

First we describe studies resulting in dose descriptors lower than 100 mg boric acid/kg bw (18 mg B/kg bw/day). Mice were exposed to boric acid at 1.2 mg/L drinking water (0.2 mg/kg bw/day[3] equal to 0.035 mg B/kg bw/day) for 5 days. This induced a body weight decrease of 28% (Aysan et al., 2013). In a follow-up study, the 28% body weight loss was accompanied by changes in cholesterol and a range of other biochemical markers. No histopathologic changes were observed (Aysan et al., 2011).

Reproductive toxicity has been a focus point of many studies. Rats were given boric acid at 5, 10, or 20 mg B/kg bw/day by oral gavage from gestation days 6–21. Then, offspring were dosed at the same levels from postnatal days 1–28. There were transient low incidences of umbilical hernia as well as reduced weight in the pups at the highest dose, and A No-Observed-Adverse-Effect Level ($NOAEL_{reduced\ pup\ weight}$) of 10 mg B/kg bw (Watson et al., 2020). Boric acid was administered in feed to time-mated rats on gestational days 0–20 at estimated dose levels between 3 and 25 mg B/kg bw/day. The NOAEL was set to 9.6 mg B/kg bw/day (=55 mg boric acid/kg bw/day) based on foetal skeletal effects (Price, 1996a). In a similar setup, a 10 mg dose was determined to be the NOAEL for developmental toxicity based on decreased offspring body weight and increased incidence of rib abnormalities in offspring (Price et al., 1998). Pregnant mice were given boric acid at 43, 79, or 176 mg B/kg bw/day throughout gestation. Pregnant rats were given this compound at 14, 29, or 58 mg B/kg bw/day. In mice, the lowest dose, 43 mg B/kg bw, could be considered a maternal NOAEL based on renal histopathological effects. Toxicity to the embryos/foetuses was seen in all rat groups, and 14 mg B/kg bw/day could be considered a Lowest-Observed-Adverse-effect Level (LOAEL) (Heindel, 1992). In a similar setup, mice were given 43, 79, or 176 mg B/kg bw day of boric acid throughout gestation; rats were given doses of 14, 29, or 58 mg B/kg bw; and rabbits were dosed with 11, 22, or 44 mg/kg bw. The authors reported a NOAEL of 43 mg B/kg bw in mice based on decreased foetal weight, whereas effects in the form of increased renal lesions were seen at this dose in mothers and thus suggests a maternal LOAEL of 43 mg B/kg bw. In rats, the lowest dose, 14 mg B/kg bw/day, was a LOAEL

[2] Using an EFSA conversion factor of 0.12 for subacute studies (EFSA, 2012).

[3] Using an EFSA default value for subacute studies of 0.18 for conversion of a drinking water concentration (mg/L) into daily dose (mg/kg bw/day) (EFSA and Committee, 2012).

in foetuses based on decreased body weight; in rat mothers, this dose was considered to be a NOAEL based on increased liver and kidney weights at the next higher dose. In rabbits, both the maternal and embryonic/foetal NOAEL was 22 mg B/kg bw/day based on a range of effects including decreased weight gain in mothers and increased prenatal mortality and increased number of malformations in the offspring (Heindel et al., 1994). In another similar study, rabbits were orally dosed with boric acid at 11, 22, or 44 mg B/kg (bw)/day on gestational days 6–19. It was unclear whether there was maternal or developmental toxicity at the two lowest doses, whereas some maternal effects as well as severe developmental effects were seen at the highest dose (44 mg B/kg bw/day) (Price, 1996b).

A range of studies found dose descriptors to be higher than 100 mg boric acid/kg bw/day (18 mg B/kg bw/day) it seems as if the effects on sperm endpoints are observed at these higher levels. Rats were given boric acid at 22, 44, or 88 mg B/kg bw/day for 2 or 4 weeks. No effects were seen on organ weights of the reproductive system, nor on behavioural effects. The sperm count and motility rate were decreased at the two highest doses at 4 weeks of exposure, whereas retention of step 19 spermatids of stages IX to XI was seen at the highest dose (88 mg B/kg bw/day) (Kudo et al., 2000). Rats were administered boric acid by oral gavage at 53 or 88 mg B/kg bw for 2 or 4 weeks. Reproductive effects including reduced testes and epididymis weights and histologic changes were seen at both dose levels, providing a LOEAL of 53 mg B/kg bw/day (Fukuda et al., 2000). In male rats, a NOAEL of 88 mg B/kg bw was seen for boric acid based on effects on spermiation and sperm quality (Linder et al., 1990). In another study in rats, a NOAEL of 95 mg B/kg bw was seen based on atrophic changes in the testes after 9 weeks of administering boric acid in feed (Ku et al., 1993).

6. Genotoxicity and carcinogenicity

In the following sections, we gathered the knowledge on the genotoxic potential of boron-containing compounds. To do that we supplement the available *in vivo* data with data from *in vitro* studies. The reason for including the latter is that genotoxicity is often incited as mechanisms inside single cells, justifying the inclusion of single cell studies on this endpoint. The details of each study in tabulated form are provided in Supplementary Materials Tables S1 to S4.

6.1. Data from studies with humans

Genotoxicity was not affected when measured by comet assay in lymphocytes of women living in boron-rich areas in Turkey compared with women who live in low- and medium-boron exposure areas, and micronuclei induction in buccal cells was even lower in the boron-rich areas compared with the low ones (Başaran et al., 2019a). In another study from the same author group, comet and micronucleus assays were used to evaluate potential DNA damage in blood, sperm, and buccal cells from 212 men occupationally exposed to boric acid in Bandırma, Turkey. No significant increases were seen in DNA strand breaks in blood and sperm from residents who were exposed to boron. This was both observed occupationally and environmentally (in so-called over--exposure group, high-exposure group, medium-exposure group and low-exposure group; all compared to a very low-exposure group). In contrast, micronuclei formation was increased in buccal cells in the over-exposure group. When evaluating abnormal cells, other than micronuclei in buccal mucosa cells, no differences were found among the groups. Notably, no correlations were found between blood levels of boric acid and the genotoxicity endpoints (Başaran et al., 2019b). In another study in a Turkish population, 30 women in a boron-rich area were compared with 30 women in a boron-poor area (Korkmaz et al., 2007). Micronuclei frequencies in buccal cells from the women were not significantly different between the two areas. In a study from China, 192 men from high and low environmental boron areas were compared. No differences were observed in semen DNA integrity measures in men from high and low environmental boron areas (Robbins et al., 2010).

6.2. In vitro bacterial assays

Boric acid was tested in *Salmonella typhimurium* strains TA100, TA1535, TA98 and TA1537 in the presence and absence of metabolic activation at boric acid concentrations up to 1820 μg/plate. No induction of revertants was observed in the four strains (National Toxicology Program, 1987). Boric acid was also negative in strains TA1535, TA1537, TA98, and TA100 in the presence and absence of metabolic activation (Haworth et al., 1983). Finally, boric acid and borax were negative in TA98 and TA100 strains at concentrations up to 100 μg/plate in the presence and absence of metabolic activation (Benson et al., 1984).

Thirteen boronic acids were tested for mutagenicity in *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, as well as in *Escherichia coli*. Compound concentrations were as high as 5000 μg/plate in the absence and presence of metabolic activation. Twelve of the 13 compounds were found to be mutagenic; all compounds, but one, were active only in TA100 and/or WP2uvrA, and did not require metabolic activation. One exception had a weak mutagenic effect in TA1537 in the presence of metabolic activation. Further results on two compounds that were mutagenic in both TA100 and WP2uvrA showed no evidence of DNA-adduct formation, as measured using ^{32}P-post-labelling (O'Donovan et al., 2011). Five boron-containing compounds were all negative in the *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and in *Escherichia coli* WP2uvrA. Each compound was tested in five concentrations, varying for each compound from low concentrations (0.05–15 μg/plate) to higher concentrations (5–5000 μg/plate) (Ciaravino et al., 2013). Sodium perborate was shown to interact with DNA in the *Escherichia coli* Pol A assay, likely involving the formation of hydrogen peroxide (Rosenkranz, 1973). A natural fructo-boron found in plants, and a natural source of boron in the human diet, was not mutagenic in *Salmonella typhimurium* at concentrations up to 5000 μg/plate (Marone et al., 2016).

6.3. In vitro mammalian assays

Concerning boric acid and borax, a range of *in vitro* studies have been conducted: boric acid was tested for its effect on mutation frequency in L5178Y mouse lymphoma cells, and sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, both in the presence and absence of metabolic activation. All three assays showed negative results (National Toxicology Program, 1987). Boric acid was also negative in another mutation frequency assay in L5178Y mouse lymphoma cells at concentrations up to 5000 μg/mL (McGregor et al., 1988). Boric acid and borax were tested in blood lymphocytes at levels up to 10 μM. No effect was seen on chromosomal aberrations or micronuclei formation (Turkez, 2008). Boric acid and borax were also tested together with TiO_2 particles, and TiO_2-induced DNA damage was decreased significantly by the presence of boric acid and borax. Boric acid and borax were tested for genotoxicity in human lymphocytes. There were no inductions of sister-chromatid exchanges, micronuclei or chromosomal aberrations at concentrations up to 10 μg/mL. In addition, both compounds decreased vanadium-induced genotoxicity (Geyikoglu and Turkez, 2008). Boric acid was tested for micronuclei formation and DNA strand breaks in V79 hamster lung fibroblast cells. No DNA damage was observed. Boric acid was also tested co-incubated with lead chloride or cadmium chloride, and boric acid decreased the genotoxic effects of the two compounds (Ustündağ et al., 2014). Boric acid and borax were tested in erythrocytes from human blood up to 500 μg/mL. Neither compound was genotoxic in sister-chromatid exchange, micronucleus or chromosomal aberration assays. (Türkez et al., 2007). Borax ore, refined borax, and kernite ore (a sodium borate hydroxide mineral, repeating units of: $Na_2B_4O_6(OH)_2{\cdot}3H_2O$) were tested for their mutagenicity (oubain resistance) in human fibroblasts and C3H/10T1/2 cells up to

3.2 mg/mL and were negative in this assay. In contrast, kernite ore induced a mutagenic response at 3.2 mg/mL in an assay detecting mutations in V79 Chinese hamster cells, whereas borax ore and refined borax were negative (Landolph, 1985). Boric acid did not induce micronuclei or sister chromatid exchanges in human lymphocytes at concentrations up to 20 ppm and in addition boric acid decreased the genotoxicity caused by aflatoxin B1 (Turkez and Geyikoglu, 2010). In another study of boric acid, no micronuclei or sister chromatid exchanges were induced in human lymphocytes at 2.5 or 5 mg/L (Turkez et al., 2010). Boric acid induced structural chromosome aberrations, but not numerical aberrations in human lymphocytes at concentrations up to 1000 μg/mL There was no induction of sister chromatid exchanges (Arslan et al., 2008). Borax was investigated for the ability to induce micronuclei and sister chromatid exchanges in human lymphocytes at concentrations up to 5 ppm and no effect was observed. In addition, borax decreased the aflatoxin B1 induced genotoxicity (Turkez et al., 2012a).

Concerning other boron containing compounds, Boron oxide (B_2O_3) was tested for micronuclei formation in Chinese Hamster Ovary cells. No induction of micronuclei were observed (Albuz et al., 2019). Nine boronic acids were tested for genotoxicity in the eukaryotic GADD45a assays, BlueScreen HC and GreenScreen HC in TK6 cells. These assays, test for genetic toxicity through the induction of the human GADD45a gene. Four compounds were positive in BlueScreen HC and one compound was positive in GreenScreen HC. These positive results were observed at 1–10 mM. When metabolic activation was induced with S9, none of the compounds were positive. (Scott and Walmsley, 2015). Boron nitride nanotubes modified in various ways did not induce DNA strand breaks in A549 cells (Emanet et al., 2015). Boron nitride nanotubes were genotoxic at low but not high concentrations in the comet assay in bone marrow $CD34^+$ hematopoietic progenitor cells, while in HeLa and V79 cells they exerted an effect at almost all concentrations (Çal and Bucurgat, 2019). Potassium tetraborate was tested in human blood cell cultures at concentrations between 0 and 1280 μg/mL. No genotoxicity was observed in the micronucleus or, chromosomal aberration assays (Çelikezen et al., 2014b). There was no induction of chromosomal aberrations or sister chromatid exchanges of zinc borate in human lymphocytes at concentrations up to 1280 mg/L (Çelikezen et al., 2014a).

Five pharmaceutical boron-containing compounds were tested in the chromosome aberration assay in peripheral human lymphocytes (Ciaravino et al., 2013). Each compound was tested at seven concentrations, varying from low concentrations (2.5–10 μg/mL) to high concentrations (684–2735 μg/mL). All five compounds were negative in this assay. A fructo-boron found in plants did not induce micronuclei formation at concentrations up to 1000 μg/mL in V79 cells (Marone et al., 2016). Lithium metaborate dehydrate was tested for chromosomal damage in human blood lymphocytes. There was no induction of chromosomal aberrations or micronuclei at concentrations up to 1280 mg/L (Çelikezen et al., 2016). Borax was investigated for genotoxic potential in human lymphocytes. There was no induction of micronuclei, sister chromatid exchanges or 8-Oxo-2′-deoxyguanosine (8-OHdG) levels up to 320 mg/L (Çelikezen et al., 2015).

6.4. Data from animal studies

Boric acid was orally administered to mice for 4 or 6 weeks (115, 250 and 450 mg/kg bw/day equal to 20, 44 and 79 mg B/kg bw/day), and sperm DNA damage was measured by comet assay. There was no effect after 4 weeks, whereas a dose-dependent effect was seen after 6 weeks. In addition, boric acid induced oxidative stress in testicular tissue (Aktas et al., 2020). Boric acid and borax were given to male rats for 4 weeks (100 mg/kg diet = 18 mg B/kg diet = 2.2 mg B/kg bw/day). The DNA damage was evaluated in blood cells by comet assay. There was no increase in DNA strand breaks in the boric acid and borax groups; conversely, the data showed a slight significant decrease (Ince et al., 2010). Boric acid was investigated in adult male rats after oral exposure at 125, 250 and 500 mg/kg bw/day for 60 days (equal to 22, 44 and 88 mg B/kg bw/day). Testicular DNA fragmentation was assessed by DNA agarose gel electrophoresis. Male germ cells exposed to boric acid throughout spermatogenesis had low DNA content and low DNA damage (El-Dakdoky and Abd El-Wahab, 2013).

Borax did not increase micronuclei formation as measured in male rat hepatocytes isolated after intraperitoneal exposure for 10 days at doses of 3.25 and 13 mg/kg bw/day. Conversely, borax decreased aluminium chloride-induced micronuclei formation (Turkez et al., 2012b). In another study in male rats, boron was orally administered for 30 days at 5, 10 and 20 mg/kg bw, together with arsenic (100 mg/L via drinking water). Boron decreased arsenic-induced DNA damage (Ince et al., 2019). Some therapeutic agents in which boron is a building block were tested by the micronucleus test after oral dosage to rats; AN0128 (a borinic picolinate), AN2690 (tavaborole), AN2728, AN2898, and AN3365 were all negative in this assay (Ciaravino et al., 2013). Eight arylboronic compounds tested in rats, were not genotoxic in the micronucleus test, the Pig-a mutation assay and the comet assay (Masuda-Herrera et al., 2019).

The genotoxic and anti-genotoxic effects of boron were investigated in the somatic mutation and recombination test (SMART) in *Drosophila melanogaster*. Boron was tested in doses up to 40 mg/L and was not genotoxic. By contrast, boron significantly ameliorated the genotoxic effect of ethyl methane sulfonate, a known mutagen (Sarıkaya et al., 2016). In *Drosophila melanogaster*, boron and boron nitride nanotubes were tested at up to 10 mM. No induction of mutant clones were observed in the wing spot test, and no effects were seen in the comet assay conducted on larvae haemocytes. By contrast, boron and boron nitride nanotubes significantly decreased the genotoxic effect of potassium dichromate; and, these boron compounds also decreased the intracellular levels of reactive oxygen species (Demir and Marcos, 2018). Zebrafish were exposed to boric acid or borax at water concentrations between 1 and 64 mg/L. Both compounds induced increased DNA strand breaks in erythrocytes (Gülsoy et al., 2015).

6.5. Carcinogenicity

A 2-year-study was performed by feeding diets containing boric acid at concentrations of 2500 and 5000 ppm to groups of 50 male and 50 female mice. There was no evidence of carcinogenicity of boric acid. However, testicular atrophy and interstitial cell hyperplasia were observed in high-dose male mice (National Toxicology Program, 1987). (EFSA, 2012) (Marone et al., 2016).

6.6. Summary on genotoxicity and carcinogenicity of boron

Human studies indicated that boron-containing compounds do not exert genotoxicity. There are a few positive findings in bacterial reverse mutation assays. However, in general, *in vitro* studies point to no genotoxicity of boron-containing compounds. Numerous studies, both *in vitro* and *in vivo*, have showed that boron protects against genotoxicity. There are a few positive results of boron in *in vivo* studies; however, most studies show negative results. Overall, studies indicate that boron-containing compounds are not genotoxic. There was no evidence of the carcinogenicity of boric acid in a 2-year study in mice.

7. Hazard characterisation

Concerning the inhalation exposure pathway, in one study with a human cohort, boron-exposed workers had a decreased Y:X chromosome ratio (1.8 mg B/kg bw) (Scialli et al., 2010). Yet, other studies on human cohorts showed no changes in reproductive endpoints. Concerning animal data, in a study using a cellulose insulation product with a boric acid content of 20%, the inhalation $NOEAC_{B\ content}$ was 0.53 mg B/m^3, but notably, it cannot be excluded that the effect was mediated by

the cellulose (Pleus et al., 2018).

A range of human dermal case studies have demonstrated severe toxicity after exposure to boric acid, including mortality. Doses were not reported in detail in these case reports. Yet the blood and tissue levels reported in some studies were high compared with normal levels in humans, suggesting that high internal doses of boric acid were reached. Thus, when the boric acid concentration on the skin is high enough, severe toxicity is expected.

Oral exposure levels of boric acid of 500 mg B/kg bw in an infant and 76 mg B/kg bw in a 77-year-old man were fatal (Ishii et al., 1993; Wong et al., 1964). Non-fatal acute poisonings with boric acid in humans are reported at intake levels of 30–450 mg B/kg bw (Baker and Bogema, 1986; Pedicelli et al., 2015; Stolpmann and Hopmann, 1975; Teshima et al., 1992). Concerning animal studies, there are number of reproductive toxicity studies providing NOAELs at approximately 10 mg B/kg/bw day and higher (Price, 1996a; Price et al., 1998; Watson et al., 2020). A LOAEL of weight reduction in mice after boric acid was 0.035 mg B/kg bw/day for 5 days (Aysan et al, 2011, 2013).

Concerning genotoxicity carcinogenicity, the overall picture indicates that boron-containing compounds are not genotoxic. There was no evidence of carcinogenicity of boric acid in a 2-year study in mice. Thus, we do not evaluate cancer to be the critical effect of boron compounds.

8. Summary

The majority of toxicity data on boron are on boric acid. Boron in the form of boric acid is readily taken up over the gastrointestinal tract. Intact skin seems to pose a more effective barrier than compromised skin. Boron excretion seems to mainly occur via the urine, although after skin intoxication, it has been detected in bile and gastrointestinal contents. The toxicity data in inhalation studies are sparse. One study in rats with the inhalation of cellulose with 20% boric acid showed decreased foetal body weight. After dermal and oral exposure, boric acid has in many cases been fatal, and a range of other toxicity endpoints were activated. Concerning genotoxicity and carcinogenicity, the overall picture indicates that boron-containing compounds are not genotoxic. There was no evidence of carcinogenicity of boric acid in a 2-year study in mice. The current work combines older and recent knowledge on the toxicity of boron-compounds. Especially within recent years, a substantial number of genotoxicity studies has been published; and reproductive data with implication for the risk assessment of insulation products have been reported.

CRediT authorship contribution statement

Niels Hadrup: Conceptualization, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Marie Frederiksen:** Conceptualization, Writing - review & editing. **Anoop K. Sharma:** Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was partly financed by a grant from the Danish Working Environment Research Fund (project name Sikker-Motor; number: 29-2019-09).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2021.104873.

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