TOX/2025/46 Annex 1

TOX/2025/46 Annex 1

Executive Summary

In this guide

In this guide

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

1. Following the UK's exit from the European Union, the Drinking Water Inspectorate (DWI) is reviewing the UK regulatory standards for some chemicals in drinking water, including boron. To support this review, the UK Health Security Agency (UKHSA) sought advice of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) with respect to an appropriate health-based guidance value (HBGV) for boron.

2. The toxicity studies on boron by Heindel et al. (1992), Price et al. (1996) and Weir and Fisher (1972) have been used by a number of authoritative bodies, including the COT in 1995, as the critical studies for their health-based guidance values (HBGVs). The differences in the HBGVs derived by these bodies are due to

differences in the choice of the points of departure (POD) from these critical studies, and uncertainty factors applied.

3. The COT concluded that the most sensitive effect is reduced fetal body weight and skeletal effects. A dose of 10 mg B/kg bw/day is an appropriate POD, and should be used with the default uncertainty factor of 100 to give a tolerable daily intake (TDI) of 0.1 mg/kg bw/day.

TOX/2025/46 Annex 1

Background and scope of discussion

In this guide

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

4. The UKHSA advises the DWI on potential health risks from chemicals in drinking water. Following the UK's exit from the EU, the DWI is reviewing the regulatory standards for some chemicals in drinking water, including boron. The COT was asked to consider the available studies, the interpretations by the various authoritative bodies and determine an appropriate Tolerable Daily Intake (TDI) to support an update to the boron drinking water standard in the UK.

5. The COT previously reviewed the available toxicity data on boron and boric acid in 1994 and 1995. It determined a No Observed Adverse Effect Level (NOAEL) of 9.6 milligrams per kilogram body weight per day (mg/kg bw/day) (rounded up to 10 mg/kg bw/day) for critical adverse effects in developmental studies in rats (reduced fetal weight and skeletal effects). Applying a default safety factor of 100, the Tolerable Daily Intake (TDI) was calculated as 0.1 mg/kg bw/day (COT,1995).

Properties of boron and sources in drinking water

In this guide

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

6. Boron (CAS No. 7440-42-8) is a naturally occurring element in the earth’s crust. Common borate compounds include boric acid, salts of boric acid (e.g., sodium tetraborates, which are also referred to as borax), and boron oxide. Boron originates from both natural sources and anthropogenic sources (Coughlin,

1996). Natural processes like weathering contribute more significantly to environmental boron levels compared to anthropogenic activities (US EPA, 2008). Human exposure to boron through drinking water occurs primarily in areas with boron-rich aquifers or where borates are released from industrial or agricultural sources (WHO, 2009). In both water and soil, its fate is largely governed by pH, which determines whether boron exists primarily as undissociated boric acid (dominant at acidic pH) or as borate ions (dominant at alkaline pH above the pKa of 9.2) (WHO, 2009; Health Canada, 2023). The chemical and toxicological properties of boric acid and other borates are considered similar on a molar boron equivalent basis when dissolved in water or biological fluids (WHO, 2009). For further information on the properties of boron, see TOX/2025/31.

Toxicity data for boron

In this guide

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

7. The toxicity of boron has been reviewed by WHO (2009), ATSDR (2010), and Health Canada (2023). Boron toxicity primarily affects the reproductive and developmental systems, as demonstrated in both human and animal studies. In

humans, lethal cases of boron ingestion have shown effects on the liver, kidneys, central nervous system, gastrointestinal system, and skin, with death primarily attributed to respiratory failure (ATSDR, 2010; Health Canada, 2023). The minimal lethal dose of ingested boron (as boric acid) was reported to be 2–3 g in infants, 5–6 g in children, and 15–20 g in adults (WHO, 2009).

8. Prolonged exposure has been linked to gastrointestinal and renal injury, while acute high intake (≥184 mg boron/kg/day) often leads to nausea and vomiting in humans. Although boron is not considered an essential nutrient for humans, low levels may confer some benefits to bone health and cognitive function (ATSDR, 2010; Health Canada 2023).

9. Oral exposure animal studies have demonstrated that the reproductive system and the developing fetus are the most sensitive targets of boron toxicity. Adverse developmental effects have been identified for both acute and intermediate-duration exposures. Developmental toxicity observed in animal models, including decreased fetal weight, skeletal abnormalities (e.g., rib malformations), and visceral anomalies. Further detail on the critical studies in animals is provided below.

10. This COT evaluation focussed on the toxicity studies on boron by Heindel et al. (1992), Price et al. (1996) and Weir and Fisher (1972) which were used by authoritative bodies as the critical studies for their health-based guidance values. Other toxicity studies showing effects at similar dose levels were also considered. The table presented in Annex A, summarises the findings of the different studies.

Summary of the Heindel et al. (1992) study

11. While the Heindel et al. (1992) paper states only that is was conducted under contract to the National Toxicology Program and the National Institute of Environmental Health Sciences (NTP/NIEHS), the follow up paper (Price et al. 1996) reports funding under the sponsorship of U.S. Borax Inc.

12. Heindel et al. (1992) conducted studies involving timed-mated Sprague-Dawley rats (29 per group) fed diets containing 0, 0.1, 0.2, or 0.4% boric acid from gestation day (GD) 0 to 20. The estimated boric acid doses were 0, 78, 163, and 330 mg/kg bw/day (0, 13.6, 28.5, and 57.7 mg B/kg bw/day). Additional groups of 14 rats received 0 or 0.8% boric acid (539 mg/kg bw/day or 94.2 mg B/kg bw/day) from GD 6 to 15 to minimize preimplantation loss and early embryo lethality identified in preliminary studies.

13. **Maternal Findings:** On GD 12-20, food intake increased by 5-7% at 0.2% and 0.4% boric acid, whereas water consumption remained unaffected. Food and water intake decreased at 0.8% on GD 6–9 and increased on GD 15–18. Treatment had no effect on the pregnancy rates (90–100%). Increased relative liver and kidney weights (0.2% and higher), increased absolute kidney weight (0.8%), and reduced body weight gain (0.4% and higher) were among the dose-related maternal effects. Corrected body weight gain was unaffected except for an increase at 0.4%. Maternal kidneys showed minimal nephropathy, but it was not dose dependent.

14. **Fetal Findings:** Prenatal mortality increased at 0.8% boric acid, with more resorptions and late fetal deaths per litter, and fewer live fetuses per litter. Fetal body weight decreased in a dose-dependent manner, with weights at 94%, 87%, 63%, and 46% of controls for 0.1%, 0.2%, 0.4%, and 0.8%, respectively. Malformations were significantly increased at 0.2% and higher, primarily affecting the eyes, CNS, cardiovascular system, and axial skeleton. Common malformations included brain ventricle enlargement and rib XIII agenesis/shortening. Skeletal variations such as wavy ribs were observed, especially at 0.8%.

15. The authors concluded a maternal LOAEL of 0.2% boric acid (28.5 mg B/kg bw/day), with a maternal NOAEL of 0.1% (13.6 mg B/kg bw/day) and a fetal LOAEL of 0.1% boric acid (13.6 mg B/kg bw/day), with no NOAEL identified.

Summary of the Price et al. (1996) study

16. The Price et al. (1996) study was conducted as a follow-up to the Heindel et al. (1992) study, addressing its limitation of not identifying a fetal NOAEL. The Price et al (1996) paper states “This laboratory investigation was conducted at Research Triangle Institute under the sponsorship of U.S. Borax Inc”.

17. Price et al. investigated the effects of dietary boric acid (0, 0.025, 0.05, 0.075, 0.1, and 0.2%) on timed-mated CD rats (60 per group) during GD 0-20. The calculated boric acid doses were 19, 36, 55, 76, and 143 mg/kg/day (3.3, 6.3, 9.6, 13.3, and 25 mg B/kg bw/day). The study comprised two phases with 14-17 rats per group per phase per replicate for Phase I. The study does not clearly state the number of rats assessed in Phase II.

18. **Phase I - Teratology Evaluation:** This phase was terminated on GD 20 when uterine contents were evaluated. No maternal deaths or clinical symptoms were observed across any dose groups during this phase. Maternal body weights were comparable among groups throughout most of gestation, but

trend analysis showed statistically significant decreases in maternal body weight (on GD 19 and GD 20) and weight gain (for GD 15-18 and GD 0-20) associated with higher doses. Corrected maternal weight gain (gestational weight gain minus gravid uterine weight) remained unaffected. Water intake increased in exposed groups after GD 15. Additionally, the number of ovarian corpora lutea, uterine implantation sites, and the percentage of preimplantation loss were unaffected by boric acid exposure.

19. **Phase 1 - Offspring Findings:** Offspring body weights on GD 20 were significantly reduced in the 13.3 and 25 mg B/kg bw/day groups, with weights in the dose groups being 99%, 98%, 97%, 94%, and 88% of control values for the low to high doses, respectively. No treatment-related increases in external or visceral malformations or variations were noted when evaluated either collectively or individually. However, skeletal malformations and variations assessed collectively showed a significant increase in the percentage of affected fetuses per litter. Dose-dependent increases were specifically observed for short rib XIII, classified as a malformation, and for wavy rib or wavy rib cartilage, categorized as variations. Statistical analysis confirmed significant increases in short rib XIII and wavy rib incidence in the 13.3 and 25 mg B/kg bw/day groups compared to controls.

20. For Phase I, the lowest observed adverse effect level (LOAEL) was determined to be 0.1% boric acid (13.3 mg B/kg bw/day) based on decreased fetal body weight. The NOAEL was established at 0.075% boric acid (9.6 mg B/kg bw/day).

21. **Phase II - Postnatal Evaluation:** In Phase II, dams were allowed to deliver and rear their litters until postnatal day (PND) 21. The calculated average boric acid doses for these dams were 19, 37, 56, 74, and 145 mg/kg bw/day (3.2, 6.5, 9.7, 12.9, and 25.3 mg B/kg bw/day). This phase was designed to evaluate whether skeletal defects observed in control and exposed pups in Phase I persisted or changed during the first 21 days postnatally. Among live-born pups, a significant trend test revealed an increased number and percentage of dead pups between PND 0 and 4, particularly in the high-dose group. However, this increase in early postnatal mortality was not significantly different from controls and fell within the range of control values recorded in other studies from the same laboratory. Between PND 4 and 21, no further increases in mortality were observed.

22. On PND 0, the initiation of Phase II, boric acid exposure did not significantly affect the body weight of offspring across dose groups, with weights

at 102%, 101%, 99%, 101%, and 100% of control values for the low- to high-dose groups, respectively. Body weights remained unaffected through to termination of Phase II on PND 21, indicating that fetal body weight deficits observed during gestation did not persist into the postnatal period.

23. The percentage of pups per litter exhibiting short rib XIII remained elevated on PND 21 in the highest dose group (0.2% boric acid, 25.3 mg B/kg bw/day). However, no instances of wavy ribs were observed on PND 21, and neither treated nor control pups exhibited an extra rib on lumbar I.

24. Based on the findings, the authors reported the NOAEL for Phase II to be 12.9 mg B/kg bw/day, while the lowest observed adverse effect level (LOAEL) was 25.3 mg B/kg bw/day.

Summary of the Weir and Fisher (1972) paper

25. The sub-chronic and chronic toxicity of borax and boric acid has been studied in rats and dogs administered these compounds in the diet (Weir and Fisher, 1972). While no funding is reported, references are made to work by the U.S. Borax Research Corp.

26. **Sub-chronic Oral Toxicity in SD Rats:** Groups of 10 Sprague-Dawley rats per sex per dose were fed diets containing borax or boric acid for 90 days at concentrations of 0, 52.5, 175, 525, 1750, and 5250 ppm boron (equivalent to approximately 0, 2.6, 8.8, 26.3, 87.5, and 262.5 mg B/kg bw/day, based on a food intake factor of 0.05 (IPCS, 2009)).

27. Both borax and boric acid produced 100% mortality at the highest dose and complete atrophy of the testes in all males fed diets containing 87.5 mg B/kg bw/day. Toxic effects at the two highest doses (87.5 mg B/kg bw/day and 262.5 mg B/kg bw/day) included rapid breathing, eye inflammation, paw swelling, and skin desquamation on paws and tails. At 87.5 mg B/kg bw/day, significant ($p<0.05$) reductions in body weight and the weights of the liver, kidneys, spleen, and testes were observed. Lower doses showed inconsistent organ weight changes and were not corroborated in the subsequent chronic studies summarised in the paper.

28. Microscopic analysis revealed complete testicular atrophy at 87.5 mg B/kg bw/day for all males and partial atrophy at 26.3 mg B/kg bw/day in four males fed borax and one fed boric acid.

29. The authors identified a NOAEL of 8.8 mg B/kg bw/day based on testicular atrophy and a LOAEL of 26.3 mg B/kg bw/day for systemic toxicity in rats after sub chronic dietary exposure study.

30. **Sub-chronic Oral Toxicity in Beagle Dogs:** Groups of beagle dogs (5/sex/dose/compound) were administered borax or boric acid for 90 days at dietary levels of 17.5, 175, and 1750 ppm boron (male: 0.33, 3.9 and 30.4 mg B/kg bw/day; female: 0.24, 2.5 and 21.8 mg B/kg bw/day) and compared with an untreated control group of 5 dogs/sex (Weir and Fisher, 1972; U.S. Borax Research Corp., 1963).

31. The testes were the primary target of boron toxicity. Microscopic pathology revealed severe testicular atrophy in all high-dose male dogs, with complete degeneration of the spermatogenic epithelium in 4/5 cases. No testicular lesions were found in the lower-dose groups.

32. Haematological effects were also observed in high-dose dogs. Decreases were found for both haematocrit (15 and 6% for males and females, respectively) and haemoglobin (11% for both males and females) at study termination in borax-treated dogs. Pathological examination revealed accumulation of hemosiderin pigment in the liver, spleen, and kidney, indicating breakdown of red blood cells, in males and females treated with borax or boric acid.

33. This study identified a LOAEL of 1750 ppm boron (male: 30.4 mg B/kg bw/day; female: 21.8 mg B/kg bw/day) and a NOAEL of 175 ppm boron (male: 3.9 mg B/kg bw/day; female: 2.5 mg B/kg bw/day) based on testicular atrophy and haemoglobin destruction in dogs following sub chronic exposure.

34. **Chronic Oral Toxicity in SD Rats:** Sprague-Dawley rats were fed a diet containing 0, 117, 350, or 1170 ppm boron as borax or boric acid for 2 years (approximately 0, 5.9, 17.5, or 58.5 mg B/kg bw/day). There were 70 rats/sex in the control groups and 35/sex in the groups fed boron compounds.

35. At high dose, rats receiving both boron compounds had decreased food consumption during the first 13 weeks of study and suppressed growth throughout the study. Signs of toxicity at this exposure level included swelling and desquamation of the paws, scaly tails, inflammation of the eyelids, and bloody discharge from the eyes. Testicular atrophy was observed in all high-dose males at 6, 12, and 24 months. The seminiferous epithelium was atrophied, and the tubular size in the testes was decreased. Testes weights and testes:body weight ratios were significantly ($p<0.05$) decreased. Brain and thyroid:body

weight ratios were significantly ($p<0.05$) increased at 1170 ppm. No treatment-related effects were observed in rats receiving 350 or 117 ppm boron as borax or boric acid.

36. This study identified a LOAEL of 1170 ppm (58.5 mg B/kg bw/day) and a NOAEL of 350 ppm (17.5 mg B/kg bw/day) for testicular effects.

37. **Chronic Oral Toxicity in Beagle Dogs:** Groups of beagle dogs (4/sex/dose/compound) were administered borax or boric acid in the diet at concentrations of 0, 58, 117, and 350 ppm boron (0, 1.4, 2.9, and 8.8 mg B/kg bw/day) for 104 weeks (Weir and Fisher, 1972; U.S. Borax Research Corp., 1966). There was a 52-week interim sacrifice and a 13-week "recovery" period after 104 weeks on test article for some dogs. Four male dogs served as controls for the borax and boric acid dosed animals. One male control dog was sacrificed after 52 weeks, two male control dogs were sacrificed after 104 weeks, and one was sacrificed after the 13-week recovery period with 104 weeks of treatment. The one male control dog sacrificed after the 13-week recovery period demonstrated testicular atrophy. Sperm samples used for counts and motility testing were taken only on the control and high-dose male dogs prior to the 2-year sacrifice.

38. At a dose level of 8.8 mg B/kg bw/day in the form of boric acid, one dog sacrificed at 104 weeks had testicular atrophy. Two semen evaluations (taken after 24 months treatment) were performed on dogs treated at the highest dose (8.8 mg B/kg bw/day). Two of two borax treated animals had samples that were azoospermic and had no motility, while one of two boric acid treated animals had samples that were azoospermic. The authors reported that there did not appear to be any definitive test article effect on any parameter examined. The study pathologist considered the histopathological findings to be "not compound-induced" and tumours were not reported.

39. In a follow-up to this study, groups of beagle dogs (4/sex/dose/compound) were given borax or boric acid in the diet at concentrations of 0 and 1170 ppm boron (0 and 29.2 mg B/kg bw/day) for up to 38 weeks (Weir and Fisher, 1972; U.S. Borax Research Corp., 1967). Exposure was stopped at 38 weeks; at this time, one animal from each treated group was sacrificed and the remaining animal from each treated group was placed on the control diet for a 25-day recovery period prior to sacrifice. New control dogs (4 males) were used for this follow up study. Of these control animals, two were sacrificed at 26 weeks and two at 38 weeks. At the 26-week sacrifice, one of two had spermatogenesis and (5%) atrophy. One was reported as normal. At 38 weeks, one had decreased spermatogenesis, and the other had testicular

atrophy.

40. The treated dogs had approximately 11% decrease in the rate of weight gain when compared with control animals, throughout the study. Interim sacrifice of two animals from each group at 26 weeks revealed severe testicular atrophy and spermatogenic arrest in male dogs treated with either boron compound. Testes weight, testes:body weight ratio, and testes:brain weight ratios were all decreased. Effects on other organs were not observed.

41. After the 25-day recovery period, testes weight and testes weight:body weight ratio were similar to controls in both boron-treated males, and microscopic examination revealed the presence of moderately active spermatogenic epithelium in one of the dogs. The researchers suggested that this finding, although based on a single animal, indicates that boron-induced testicular degeneration in dogs may be reversible upon cessation of exposure.

42. When the 2-year and 38-week dog studies are considered together, the NOAEL and LOAEL for systemic toxicity can be established at 8.8 and 29.2 mg B/kg bw/day, respectively, based on testicular atrophy and spermatogenic arrest.

43. **Multigenerational study in SD rats:** In a multigenerational study, Weir and Fisher (1972) administered 0, 117, 350, or 1170 ppm boron (approximately 0, 5.9, 17.5, or 58.5 mg B/kg bw/day) as borax or boric acid in the diet to groups of 8 male and 16 female Sprague-Dawley rats.

44. No adverse effects on reproduction or gross pathology were observed in the rats dosed with 5.9 or 17.5 mg B/kg bw/day that were examined to the F3 generation. Litter size, weights of progeny, and appearance were normal when compared with controls. The test groups receiving 58.5 mg B/kg bw/day boron from either compound were found to be sterile. In these groups, males showed lack of spermatozoa in atrophied testes, and females showed decreased ovulation in the majority of the ovaries examined. An attempt to obtain litters by mating the treated females with the males fed only the control diet was not successful.

45. A LOAEL of 58.5 mg B/kg bw/day and a NOAEL of 17.5 mg B/kg bw/day based on sterility and testicular atrophy were identified from this study.

Additional Toxicology Studies

46. This section summarises several other studies that have contributed to the understanding of the toxic effects of boron across species and exposure

durations, which show effects at similar dose levels to the Heindel et al (1992), Price et al. (1996) and Weir and Fisher (1972) studies, and drawn from the ATSDR (2010) review.

47. Dixon et al. (1976) studied the effects of sodium tetraborate on reproduction in male rats following acute and subchronic exposure. In the acute study, adult male Sprague–Dawley rats (10 animals per group) were given single oral doses of sodium tetraborate at 0, 45, 150 or 450 mg boron/kg bw. Fertility was assessed by serial mating trials in which each male was mated with a series of untreated virgin females in sequential 7 day periods (for up to 70 days). The females were sacrificed 9 days after the end of their breeding periods (when they could be 9–16 days pregnant), and uteri and fetuses were examined, though no evaluation is reported. Male rats were sacrificed on days 1 and 7, and at subsequent 7-day intervals, for histopathological examination of the testes. No effect on male fertility was found at any dose in this study. Testicular lesions were not reported. In the sub-chronic study, rats were exposed to drinking water boron concentrations of 0.3, 1.0 and 6.0 (maximum dose equivalent to 0.84 mg B/kg bw/day). Groups were selected randomly at 30, 60 and 90 days and noted for body weight and weight of the testis, prostate, and seminal vesicles as well as changes in serum chemistry (sodium, potassium, chloride, carbon dioxide, total proteins, albumin, calcium, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), glucose and serum glutamic-oxalic transaminase (SGOT), serum glutamic pyruvate transaminase, fructose, zinc and phosphate). Boron treatment did not affect LH and FSH in plasma. The sub-chronic tests failed to indicate any reproductive effects, changes in serum chemistry and body weight and weight of the testis, prostate, and seminal vesicles. For this study, a US EPA evaluation of boron reported a NOAEL of 450 mg boron/kg bw for reproductive effects in male rats following single-dose oral exposure.

48. A study by Lee et al. (1978) investigated the effects of dietary boron exposure on groups of 18 male Sprague-Dawley rats by administering 0, 500, 1000, and 2000 ppm of boron (as borax) in food for 30 to 60 days (equivalent to 0, 2.8, 5.7, and 11.3 mg B/kg bw/day). Rats receiving 500 ppm (2.8 mg B/kg bw/day) showed no significant adverse effects. However, exposure to 1000 and 2000 ppm resulted in testicular atrophy, germ cell depletion, reduced seminiferous tubular diameter, and increased testicular boron levels. These morphological changes were linked to decreased activities of post-meiotic germ cell markers, while other enzyme activities increased, likely due to the relative enrichment of Sertoli cells and spermatogonia. Hormonal analysis revealed elevated plasma FSH, variable LH changes, and normal testosterone levels. Serial

mating studies demonstrated dose-dependent reductions in fertility, with prolonged infertility at the highest dose. Rats exposed to 2000 ppm (11.3 mg B/kg bw/day) exhibited persistent germinal aplasia and infertility, lasting at least 8 months post-exposure. The NOAEL was determined to be 2.8 mg B/kg bw/day, based on testicular atrophy. These findings suggest that boron accumulation in the testes leads to progressive germ cell depletion and long-term reproductive dysfunction.

49. Dixon et al. (1979) investigated the effects of dietary boron exposure to boron on male Sprague-Dawley rats by administering 0, 500, 1000, and 2000 ppm of boron (as borax) in food for 30 to 60 days (equivalent to 0, 25, 50, and 100 mg B/kg bw/day). Eighteen male rats per group were examined for correlations between enzyme activity (hyaluronidase (H), lactate dehydrogenase isoenzyme-X (LDH-X), dehydrogenases of sorbitol (SDH), a-glycerophosphate (GPDH), glucose--phosphate (G6PDH), malate (MDH), glyceraldehyde-3-phosphate (G3PDH), and isocitrate (ICDH)) and testicular histology and androgen activities of the male accessory organs. There was a significant decrease in tubular diameter across all the doses in the 60-day treatment groups. Male fertility was unaffected at 500 ppm. There was significant loss of germinal elements, testicular atrophy, reduced spermatocytes and spermatogenic cells at 1000 ppm. At 2000 ppm, several germinal aplasia, testicular atrophy, infertility and irreversible damage was noted in some cases. There was no dose-related decrease in litter size or fetal death in utero. Plasma FSH levels were elevated at higher doses, however, LH and testosterone remained unchanged. No dominant lethal effects were observed, and a testicular boron concentration of 6-8 ppm was associated with infertility. Overall, the authors established a NOAEL of 25 mg B/kg bw/day based on dose-related tubular germinal aplasia, which was noted to be reversible at low doses.

50. Seal and Weeth (1980) conducted a 70-day study on Long-Evans hooded rats to further evaluate boron toxicity in drinking water and investigate its physiological effects at high concentrations. Male rats (15 per group) were given 0, 150, or 300 mg B/L, corresponding to recalculated doses of 0, 23.7, and 44.7 mg B/kg bw/day. Rats exposed to 150 mg B/L showed a 7.8% reduction in body weight, while those at 300 mg B/L had a 19.8% decrease. High-dose rats exhibited atrophic scrotal sacs, coarse fur, and elongated toenails. Testes and seminal vesicle weights significantly reduced, and spermatogenesis was severely impaired at 300 mg B/L, with only 3 out of 15 rats producing spermatozoa. Plasma protein and triglycerides were reduced at high doses, and bone calcium levels decreased at 300 mg B/L, indicating possible bone metabolism disruption.

The study identified 23.7 mg/kg bw/day as the lowest observed adverse effect level (LOAEL) based on impaired spermatogenesis.

51. Settimi et al. (1982) studied the effects of sodium tetraborate exposure in 2 month old Wistar rats. Male rats (20 per dose group) received either 0 or 3 g/L sodium tetraborate (0 – 20.8 mg B/kg bw/day as reported by ATSDR, 2010) in drinking water for 3 to 14 weeks. The study found increased cerebral succinate dehydrogenase activity after 10 and 14 weeks, along with elevated RNA concentration and acid proteinase activity in the brain at 14 weeks. In the liver, NADPH-cytochrome c reductase activity and cytochrome b5 content in the microsomal fraction decreased after 10 and 14 weeks, while cytochrome P-450 concentration was reduced at 14 weeks. There were no significant effects on body weight or liver, kidney, and testis weights compared to controls. The results support the hypothesis that the borate anion exerts its toxic effects by interfering with flavin metabolism in flavoprotein-dependent pathways.

52. Fail et al. (1991) evaluated the potential reproductive toxicity of boric acid in Swiss CD-1 mice using the Reproductive Assessment by Continuous Breeding protocol. Male and female mice were exposed to boric acid through feed at concentrations of 0, 1000, 4500, or 9000 ppm (0, 27, 111 and 220 B/kg bw/day) for 27 weeks. Fertility effects were observed during a 14-week cohabitation period, where 4500 ppm partially reduced fertility, and 9000 ppm resulted in complete infertility, with no litters, dead or alive, produced at the highest dose. Among litters born at 4500 ppm, live litter size and body weight were significantly reduced. A crossover mating trial confirmed that males were the most affected, as 4500 ppm-exposed males mated with control females had significantly lower fertility rates and mating indices. Necropsy findings after 27 weeks of exposure showed dose-related reductions in male reproductive organ weights, increased abnormal sperm morphology, decreased sperm concentration and motility, and seminiferous tubule degeneration. In females, 4500 ppm exposure led to significantly reduced kidney/adrenal and liver weights, while kidney/adrenal weight reductions were also seen in males. Further assessment of the F1 generation, where the last litters of control and 1000 ppm females were reared to 74 days and mated within their treatment groups, showed normal fertility but decreased adjusted mean body weight in F2 pups. Overall, males were identified as the most sensitive sex for boron toxicity.

53. Harris et al. (1992) conducted a study on Swiss CD-1 mice to assess reproductive and developmental toxicity of boric acid. Male and female mice were orally exposed via gavage, with the female group receiving daily doses for 19

days and co-habited with treated male mice after 7 days to evaluate reproductive toxicity, and a second group exposed during gestation (GD 8-14) and allowed to litter for observations through to postnatal day 4 (PND 4) to assess developmental toxicity. Dose levels used were 0, 120, 400 and 1200 mg/kg/day boric acid (0, 29.8, 69.92 and 209.76 B/kg bw/day). Significant testicular toxicity, including germ cell loss and reduced testis weight, was observed at the highest dose (1200 mg/kg/day). No effects were seen on epididymal weight or sperm density. Pregnant females at high doses exhibited increased post-implantation loss, and there was a reduction in live births at the highest dose, though no neonatal mortality occurred between postnatal days 1 and 4.

54. In a study conducted by Ku et al. (1993), the reversibility of testicular lesions was evaluated in F344 rats administered boric acid in feed at concentrations of 0, 3,000, 4,500, 6,000, or 9,000 mg/kg (0, 26, 38, 52 or 68 mg B/kg bw/day) for 9 weeks. Recovery was assessed for up to 32 weeks post-treatment. Mild spermiation inhibition was observed at 3000 ppm from week 5, while 4500 ppm caused severe spermiation inhibition by week 2, leading to a 72–97% reduction in epididymal sperm count. Higher doses (6000 and 9000 ppm) resulted in progressive testicular atrophy, appearing by week 9 at 6000 ppm and as early as week 6 at 9000 ppm. Even after 32 weeks post-treatment, no recovery from testicular atrophy was observed in higher dose groups. No boron accumulation in the testes beyond levels found in blood was detected during the 9-week exposure period. Following treatment, serum and testis boron levels in all dose groups declined to background levels. Increased serum FSH and LH levels indicated a gonadotropin response to testicular damage.

55. Chapin et al. (1997) investigated whether elevated dietary boric acid levels affected bone-related parameters, including serum electrolytes, bone structure, and strength. In the first study, male rats consumed diets containing 3000, 4500, 6000, or 9000 ppm boric acid (52.5, 78.8, 105 or 157.5 mg B/kg bw/day) for nine weeks, with serum calcium, phosphorous, potassium, chloride, and boron levels monitored during and after exposure. The second study included both male and female rats consuming diets with 200, 1000, 3000, or 9000 ppm boric acid (3.5, 17.5, 52.5 or 157.5 mg B/kg bw/day) for 12 weeks, assessing serum calcium, phosphorous, and magnesium levels, bone boron concentration, and bone structure and strength. The control diet contained 20–40 ppm boric acid (no further information provided). Serum and bone boron concentrations were measured at weekly intervals and at 8, 16, 24, and 32 weeks post-exposure. Boron concentrations in bone were elevated in all treated groups, reaching up to four times the levels found in serum. Following cessation of exposure, serum and

urinary boron levels returned to control values, while boron levels in bone remained three times higher than control levels up to 32 weeks post-exposure.

56. Yoshizaki et al. (1999) conducted a three-week study on Wistar rats to evaluate the effects of boric acid on male reproductive parameters. Male rats (20 per group) received oral doses of 50, 150, and 500 mg/kg/day of boric acid (8.8, 26, 88 mg B/kg bw/day) via drinking water. Results showed that all parameters of epididymal sperm analysis were affected at the highest dose (500 mg/kg/day), with sperm number, motility, velocity, and amplitude of lateral head displacement also impacted at 150 mg/kg/day. Morphological examinations revealed seminiferous tubule atrophy and multinucleated giant cells in the testes at 500 mg/kg/day. The NOAEL in this study was 50 mg boric acid/kg bw/day (equivalent to 8.8 mg boron/kg bw/day).

57. Sabuncuoglu et al. (2006) exposed male albino Sprague–Dawley rats (24 per group) to boric acid at doses of 0, 100, 275, or 400 mg/kg bw/day (0, 17.5, 48.1 and 70 mg B/kg bw/day). Kidneys were collected on days 10, 30, and 45 following sacrifice, and kidney weights, boron concentrations, and histopathological changes were assessed. Significant boron accumulation was observed in kidney tissue across all experimental groups, with a marked decrease in boron concentration on day 45 compared to day 30. Histopathological degenerative changes, particularly in proximal tubular cells, were dose- and time-dependent. The study concluded that subacute boric acid exposure led to dose-dependent kidney tissue damage in all exposed groups.

Previous COT evaluation

In this guide

7. TOX/2025/46 Annex 1 - Discussion
8. TOX/2025/46 Annex 1 - Overall Conclusion
9. TOX/2025/46 Annex 1 - List of abbreviations
10. TOX/2025/46 Annex 1 - References

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

58. Following publication of a new WHO drinking water guideline value in 1993, which was lower than the UK regulatory limit for drinking water at the time, the COT was asked to consider the toxicity data. In 1994, the COT provisionally agreed with the WHO (1993) NOAEL of 8.8 mg/kg bw/day for boron and acknowledged that the testis was a target organ for boron toxicity. However, the COT requested further information before finalising its conclusions.

59. In 1995, the COT considered a review of borates by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) and a US National Toxicology Program (NTP) follow up to the Heindel et al., 1992 developmental toxicity study in rats (that would later be published by Price et al., 1996). The COT noted reported reduction in relative testis weight (without histological changes) following a dose of 4.4 mg/kg bw/day of boron in a 90-day oral study of boric acid in dogs (Weir and fisher 1972). However, this was not seen in a 2-year study in dogs at higher doses where no convincing evidence of testicular toxicity was observed at boron doses of 8 to 9 mg/kg bw/day (Weir and Fisher 1972). The COT considered that the dog studies reported by Weir and Fisher 1972 were unreliable due to small animal numbers in the experimental groups and inadequacies in the histopathological descriptions. The COT agreed that the NTP follow up developmental study in rats was of good quality and demonstrated a NOAEL of 9.6 mg born/kg bw/day for adverse effects of boron. Overall, the COT concluded that a NOAEL of around 10 mg/kg bw/day could be set based on the rat developmental studies.

Evaluations by other authoritative bodies

In this guide

In this guide

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

60. The evaluations conducted by various other authoritative bodies are summarised below in order of publication.

World Health Organisation (WHO, 1993)

61. In 1993, WHO derived a tolerable daily intake for boron of 0.088 mg/kg bw/day.

62. For this evaluation, the WHO considered the critical effect of boron to be testicular atrophy in a 2 year dog study (assumed to be Weir and Fisher 1972), with a NOAEL of 8.8 mg B/kg bw/day. A total uncertainty factor of 100 for interspecies and intraspecies variability was applied (WHO, 1993).

European Centre for Ecotoxicology and Toxicology of Chemical (ECETOC, 1995)

63. ECETOC considered that acute and long-term exposure studies of boron indicated that testis was a target organ. Borates were not considered to be genotoxic or carcinogenic. A risk assessment was carried out based on reproductive and developmental effects as this was considered the most sensitive endpoint.

64. The NOAEL was based on boron intake from the diet noted in the Weir and Fisher 1972, Lee et al., 1978 and Ku et al., 1993a studies in rats and the Fail et al., 1971 study in mice. The 2-year study in dogs by Weir and Fisher in 1972 was not considered for this due to several inadequacies. Based on these studies, the LOAEL for reproductive toxicity was determined to be 17.5 mg B/kg bw. The NOAEL and LOAEL for testicular changes in rodents was noted to be 17 mg B/kg bw and 26 mg B/kg bw, respectively. Developmental toxicity studies in rats (Heindel et al., 1992; Price et al.,1994), mice (Heindel et al.,1992) and rabbits (NTP, 1991) noted that rats were the most sensitive species with a NOAEL of 9.6 mg B/kg bw. Different NOAELs were determined for 3 different endpoints. Considering interspecies and intraspecies differences, the possible TDIs were calculated to be 35 mg B/day (0.583 mg/kg bw/day) for fertility, 34 mg B/day (0.567 mg/kg bw/day) for testicular effects and 19.2 mg B/day (0.32 mg/kg bw/day) for developmental effects. The TDI of 19.2 mg B/day (0.32 mg/kg bw/day) was agreed and considered adequate to protect human health.

Expert Group on Vitamins and Minerals (EVM, 2003)

65. The NOAEL of 9.6 mg/kg bw/day from the Price et al., 1996 study was used by the EVM to establish a Safe Upper Level (SUL). Reproductive toxicity was identified as the most sensitive endpoint and an uncertainty factor of 10 for inter-species variation and 6 for intra-species variation (based on a factor of 1.8 to account for variation in glomerular filtration in women and a factor of 3.2 to account for variability in toxicodynamics) as proposed by Dourson et al (1998) was used to derive a Safe Upper Level (SUL) of 0.16 mg boron/kg bw/day.

World Health Organization (WHO, 2009)

66. In 2009, WHO derived a further tolerable daily intake (TDI) for boron of 0.2 mg/kg bw/day (WHO, 2009).

67. The WHO considered the critical effect of boron to be decreased fetal body weight in rats, for which the NOAEL was 9.6 mg B/kg bw/day (Price et al., 1996). Multiple developmental end point data from the Heindel et al. (1992) and Price et al. (1996) studies were pooled and subjected to multiple benchmark dose analyses (Allen et al. 1996). The 95% lower confidence limit on the benchmark dose associated with a 5% reduction in mean fetal body weight (BMDL05) was calculated to be 10.3 mg B/kg bw/day. This BMDL05 is close to the Price et al.

(1996) NOAEL of 9.6 mg B/kg bw/day. A total uncertainty factor of 60 was applied to the BMDL − 10 for interspecies variation and 6 for intraspecies variation based on a factor of 1.8 to account for variation in glomerular filtration in women and a factor of 3.2 to account for variability in toxicodynamics, as proposed by Dourson et al (1998). This was used to establish a TDI of 0.17 mg/kg bw/day, rounded to 0.2 mg/kg bw/day.

Agency for Toxic Substances and Disease Registry (ATSDR, 2010)

68. The ATSDR has derived an intermediate-duration oral Minimal Risk Level (MRL) for boron of 0.2 mg/kg bw/day. An MRL is an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure; the intermediate duration used in this instance covers exposures between 15 and 365 days.

69. ATSDR noted that the available intermediate duration oral studies identify the developing fetus as the most sensitive target of toxicity. Two studies in rats (Heindel et al. 1992; Price et al. 1996) identified LOAELs of 13–13.6 mg B/kg bw/day for decreases in fetal body weight and skeletal malformations (only identified in the Price et al. 1996 study). These LOAELs are lower than the NOAEL of 30 mg B/kg bw/day identified for reproductive toxicity in a 3-generation study (Weir and Fisher 1972) and NOAELs of 35 or 45 mg B/kg bw/day for haematological and dermal effects (Weir and Fisher 1972) (ATSDR, 2010).

70. The BMDL05 of 10.3 mg boron/kg/day based on decreased fetal body weight in rats derived by Allen et al. 1996 (described above) was divided by a chemical-specific uncertainty factor of 66 (3.3 for toxicokinetic extrapolation from animals to humans, 3.16 for toxicodynamic extrapolation from animals to humans, 2.0 for variability in human toxicokinetics, and 3.16 for variability in human toxicodynamics) resulting in an intermediate-duration oral MRL of 0.2 mg B/kg bw/day (rounded value).

European Food Safety Authority (EFSA, 2013)

71. In 2013, the EFSA also considered that the male reproductive system in animals is a target for boron toxicity. From a developmental study in rats (Price et al., 1996a), a NOAEL of 9.6 mg B/kg bw/day for developmental toxicity (decreased fetal weight) was identified. Application of a total uncertainty factor of 60 (6 for

intraspecies variation based on a factor of 1.8 to account for variation in glomerular filtration in women and a factor of 3.2 to account for variability in toxicodynamics and 10 for interspecies variation) produced a TDI of 0.16 mg/kg bw/day (EFSA 2013).

Health Canada

72. A BMDL05 of 2.90 mg/kg bw/day was estimated for the testicular effects (decreased testicular weight) in dogs in the study by Weir and Fisher 1972. A total uncertainty factor of 300 (10 for interspecies variability, 10 for intraspecies variability and 3 for database uncertainties, including that histological changes may occur at lower doses than those associated with testicular weight) was applied which produced a TDI of 0.01 mg/kg bw/day (Health Canada, 2023).

73. Health Canada noted that if an alternative NOAEL were used from the study in rats by Price et al., 1996, then an alternative TDI of 0.18 mg/kg bw/day could be estimated. By using the data from Price et al., (1996) study based on decreased fetal body weight, Health Canada derived a BMDL05 of 10.6 mg B/kg bw/day. It was acknowledged that this value was consistent with the BMDL05 established by Allen et al. (1996) using the same dataset. A total uncertainty factor of 60 (6 for intraspecies variability, 10 for interspecies variability) was applied to this BMDL05, which produced a TDI of 0.18 mg/kg bw/day (Health Canada, 2023).

Discussion

In this guide

7. TOX/2025/46 Annex 1 - Discussion
8. TOX/2025/46 Annex 1 - Overall Conclusion
9. TOX/2025/46 Annex 1 - List of abbreviations
10. TOX/2025/46 Annex 1 - References

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

74. The Committee noted that majority of laboratory animal oral toxicity data studies were undertaken between the 1960's and the 1990's, and there was limited human epidemiological evidence at levels of boron exposure expected from drinking water.

75. The Committee considered that the developmental toxicity study in rats by Price et al. (1996) was a good and well conducted multi-generational study, which identified a NOAEL of 9.6 mg/kg bw/day for reduced fetal body weight and skeletal malformations. The available oral toxicity data across the available studies were generally consistent and similar across species in identifying reduced fetal body weight, adverse effects in the testes and developmental malformations (e.g., skeletal malformations). The COT also considered that the NOAELs reported in the later oral toxicity studies were broadly consistent at approximately 10.0 mg B/kg bw/day, as far as could be determined.

76. Several concerns were raised with respect to the Weir and Fisher, 1972 dog studies, and associated data undertaken in the 1960's by the Borax Research Corporation, which Health Canada had considered, but the COT had not further evaluated as they are not publicly available. The dog studies used a small sample size (approximately 4 per group) and provided no information on the age of the dogs. The Committee considered that this impaired the interpretation of the reported atrophy of the testes because the testicular epithelium could be incompletely developed in sexually immature dogs making it difficult to distinguish from testicular atrophy. Overall, the COT concluded that the dog oral toxicity studies were inadequate and not suitable for identifying a POD.

77. The Committee agreed with the broad consensus among authoritative bodies on using Price et al study as the basis for the POD (ECETOC, 1995; EFSA, 2013; EVM, 2003; WHO, 2009). Some authoritative organizations had used benchmark dose (BMD) modelling of the Price at al., (1996) study data, while others had used the NOAEL as a basis for their HBGV's. The COT noted that

despite developments in BMD modelling, this made little difference to the resultant BMDL, and the BMDL and the study NOAEL were broadly similar. The Committee concluded that 10.0 mg B/kg bw/day was an appropriate POD, as had been concluded in the earlier COT assessment conducted in 1995.

78. In considering the uncertainty factor to use to derive a HBGV, the COT recognized that there had been consensus across several authoritative organizations in selecting a total uncertainty factor of approximately 60. However, the COT concluded that a total uncertainty factor of 100 was appropriate as this would account for the severity of the toxicity endpoints (reduced fetal weight and skeletal malformations), the extrapolation from animal to humans, and differences in toxicokinetics for different boron compounds. Applying a total uncertainty factor of 100, to the selected POD of 10.0 mg/kg bw/day would result in a TDI of 0.1 mg/kg bw/day.

Overall Conclusion

In this guide

79. Overall, the COT agreed with the broad consensus of other authoritative bodies that the Price et al., 1996 rat developmental toxicity study was the most appropriate basis for a HBGV. A dose of 10.0 mg B/kg bw/day was identified as an appropriate POD, consistent with the COT's previous assessment in 1995. Applying a default uncertainty factor of 100 to the POD results in a Tolerable Daily Intake (TDI) of 0.1 mg/kg bw/day

List of abbreviations

In this guide

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

ATSDR	Agency for Toxic Substances and Disease Registry
BMDL05	BMDL05 is the benchmark dose lower limit (BMDL) associated with a benchmark response (BMR) of 5%.

bw	Body Weight
CAS	Chemical Abstracts Service
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
DWI	Drinking Water Inspectorate
EFSA	European Food Safety Authority
GD	Gestation Day
HBGV	Health-based guidance value
LOAEL	Lowest Observed Adverse Effect Level - the lowest dose in a study at which adverse effect(s) are observed.
mg	milligram
MRL	Minimal Risk Level - an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure
NOAEL	No Observed Adverse Effect Level - the highest administered dose at which no adverse effect has been observed.
NTP	National Toxicology Program
PND	Postnatal Day
POD	Point of Departure

ppm	Parts per million
TDI	Tolerable Daily Intake - an estimate of the amount of a contaminant, expressed on a body weight basis (e.g., mg/kg body weight) that can be ingested over a lifetime without appreciable health risk.
UKHSA	UK Health Security Agency
US EPA	US Environmental Protection Agency
WHO	World Health Organization

References

In this guide

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Agency for Toxic Substances and Disease Registry (ATSDR) (2010) Toxicological profile for Boron. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. ATSDR Boron Tox Profile

Allen, B.C., Strong, P.L., Price, C.J., Hubbard, S.A. and Daston, G.P., 1996. Benchmark dose analysis of developmental toxicity in rats exposed to boric acid. Fundamental and Applied Toxicology, 32(2), pp.194-204.

Chapin, R. E., Ku, W. W., Kenney, M. A., McCoy, H., Gladen, B., Wine, R. N., Wilson, R. and Elwell, M. R., 1997. The effects of dietary boron on bone strength in rats. Fundamental and Applied Toxicology, 35, pp.205–215.

Chapin, R.E., Ku, W.W., Kenney, M.A. and McCoy, H., 1998. The effects of dietary boric acid on bone strength in rats. Biological Trace Element Research, 66, pp.395-399.

COT (Committee on Toxicity) (1995) Annual report: Boron in drinking water and food. p. 6. cotannualreport1995.pdf

Coughlin, J.R., 1996. Inorganic borates: Chemistry, human exposure, and health and regulatory guidelines. The Journal of Trace Elements in Experimental Medicine: The Official Publication of the International Society for Trace Element Research in Humans, 9(4), pp.137-151.

Dixon R.L., Lee I.P. and Sherins R.J., 1976. Methods to assess reproductive effects of environmental chemicals: studies of cadmium and boron administered orally. Environmental Health Perspectives, 13, pp.59-67.

Dixon R.L., Sherins R.J. and Lee I.P., 1979. Assessment of environmental factors affecting male fertility. Environmental Health Perspectives, 30, pp.53-68.

Dourson, M., Maier, A., Meek, B., Renwick, A., Ohanian, E., Poirier, K. (1998) Re-evaluation of toxicokinetics for data-derived uncertainty factors. Biological Trace Element Research 66, 453-463.

ECETOC, 1995. Reproductive and general toxicology of some inorganic borates and risk assessment for human beings (Technical Report No. 63).

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2013. Scientific Opinion on the re-evaluation of boric acid (E 284) and sodium tetraborate (borax) (E 285) as food additives. EFSA Journal, 11(10), p.3407. Scientific Opinion on the re-evaluation of boric acid (E 284) and sodium tetraborate (borax) (E 285) as food additives - - 2013 - EFSA Journal - Wiley Online

Library

EVM, 2003. Boron – in Safe Upper Levels for Vitamins and Minerals pages 164-171. vitmin2003.pdf

Fail, P. A., George, J. D., Seely, J. C., Grizzle, T. B. and Heindel, J. J., 1991. Reproductive toxicity of boric acid in Swiss (CD-1) mice: Assessment using the continuous breeding protocol. Fundamental and Applied Toxicology, 17, pp.225–239.

Forbes, R.M., Cooper, A.R. and Mitchell, H.H., 1954. On the occurrence of beryllium, boron, cobalt, and mercury in human tissues.

Harris, M. W., Chapin, R. E., Lockhart, A. C. and Jokinen, M. P., 1992. Assessment of a short-term reproductive and developmental toxicity screen. Fundamental and Applied Toxicology, 19, pp.186–196.

Health Canada (2023) Boron: Guidelines for drinking water quality. Health Canada, Ottawa. Guidelines for Canadian drinking water quality boron: Overview - Canada.ca

Heindel, J.J., Price, C.J., Field, E.A., Marr, M.C., Myers, C.B., Morrissey, R.E. and Schwetz, B.A., 1992. Developmental toxicity of boric acid in mice and rats. Fundamental and applied toxicology, 18(2), pp.266-277. Developmental toxicity of boric acid in mice and rats - ScienceDirect

IPCS, 2009. Principles and methods for the risk assessment of chemicals in food. Environmental Health Criteria 240, Principles and methods for the risk assessment of chemicals in food (EHC 240, 2009)

Ku, W. W., Chapin, R. E., Wine, R. N. and Gladen, B. C., 1993. Testicular toxicity of boric acid (BA): Relationship of dose to lesion development and recovery in the F344 rat. Reproductive Toxicology, 7, pp.305–319.

Lee, I. P., Sherins, R. J. and Dixon, R. L., 1978. Evidence for induction of germinal aplasia in male rats by environmental exposure to boron. Toxicology and Applied Pharmacology, 45, pp.577–590.

Murray, F.J., 1998. A comparative review of the pharmacokinetics of boric acid in rodents and humans. Biological trace element research, 66, pp.331-341.

Pahl, M.V., Culver, B.D., Strong, P.L., Murray, F.J. and Vaziri, N.D., 2001. The effect of pregnancy on renal clearance of boron in humans: a study based on normal

dietary intake of boron. Toxicological Sciences, 60(2), pp.252-256.

Price, C. J., M. C. Marr, and C. B. Myers. "Determination of the No-Observable-Adverse-Effect Level (NOAEL) for Developmental Toxicity in Sprague-Dawley (CD) Rats Exposed to Boric Acid in Feed on Gestational Days 0 to 20, and Evaluation of Postnatal Recovery through Postnatal Day 21." Research Triangle Park (NC): Research Triangle Institute (RTI Identification No. 65C-5657-20O) (1994).

Price, C.J., Strong, P.L., Marr, M.C., Myers, C.B. and Murray, F.J., 1996. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fundamental and applied toxicology, 32(2), pp.179-193. Developmental Toxicity NOAEL and Postnatal Recovery in Rats Fed Boric Acid during Gestation - ScienceDirect

Sabuncuoglu, B. T., Kocaturk, P. A., Yaman, O., Kavas, G. O., and Tekelioglu, M., 2006. Effects of subacute boric acid administration on rat kidney tissue. Clinical Toxicology, 44(3), pp.249–253.

Seal, B. S. and Weeth, H. J., 1980. Effect of boron in drinking water on the male laboratory rat. Bulletin of Environmental Contamination and Toxicology, 25, pp.782–789.

Settimi, L., Elovaara, E. and Savolainen, H., 1982. Effects of extended peroral borate ingestion on rat liver and brain. Toxicology Letters, 10, pp.219–223.

US EPA, 2008. Health effects support document for boron. Health and Ecological Criteria Division. US Environmental Protection Agency, Washington, DC.

Weir Jr, R.J. and Fisher, R.S., 1972. Toxicologic studies on borax and boric acid. Toxicology and applied pharmacology, 23(3), pp.351-364. Toxicologic studies on borax and boric acid - ScienceDirect

WHO, 1993. Boron – in Guidelines for drinking-water quality, 2nd edition: Volume 1 – Recommendations page 43-44. https://www.who.int/publications/i/item/924154460O

WHO, 2009. Boron in drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality (No. WHO/HSE/WSH/09.01/2). World Health Organization. Microsoft Word - Fourth Edition Boron Final January 2010.doc

Yoshizaki, H., Izumi, Y., Hirayama, C., Fujimoto, A., Kandori, H., Sugitani, T., and Ooshima, Y., 1999. Availability of sperm examination for male reproductive toxicities in rats treated with boric acid. The Journal of Toxicological Sciences,

24(3), pp.199–.