Toxicity data for boron

In this guide

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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.