Summary of the Weir and Fisher (1972) paper

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28. 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.

29. **Sub-chronic Oral Toxicity in SD Rats:** Weir and Fisher (1972) investigated boron toxicity in Sprague-Dawley rats. Groups of 10 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)). 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.

30. At 2.6 mg B/kg bw/day, increased weights of the brain, spleen, kidneys, and ovaries were noted in females fed borax, while females fed boric acid showed increased liver weight; no changes were observed in males. At 8.8 mg B/kg bw/day, only increased kidney weights were reported in males fed borax. However, these changes were absent at 26.3 mg B/kg bw/day for both compounds. 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.

31. 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. The organ weight changes observed at 2.6 mg B/kg bw/day were not dose-dependent and were not corroborated in subsequent chronic studies by the same researchers.

32. 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.

33. **Sub-chronic Oral Toxicity in Beagle Dogs:** Groups of beagle dogs (5/sex/dose/compound) were administered borax (sodium tetraborate decahydrate) 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). On day 68 of the study,

a high-dose male dog died as a result of complications of diarrhoea with severe congestion of the mucosa of the small and large intestines and congestion of the kidneys. No clinical signs of toxicity were evident in the other dogs. The testes were the primary target of boron toxicity.

34. At the high dose, mean testes weight was decreased 44% (9.6 g) in males fed borax and 39% (10.5 g) in males fed boric acid compared with controls (17.2 g). Also at this dose, mean testes:body weight ratio (control: 0.2%; borax: 0.1%; boric acid: 0.12%) and mean testes:brain weight ratio (control: 22%; borax: 12%) were significantly reduced. Decreased testes:body weight ratio was also observed in one dog from the mid-dose (175 ppm) boric acid group.

35. 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.

36. 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. Other effects in high-dose dogs were decreased thyroid:body weight ratio (control: 0.009%; borax: 0.006%; boric acid: 0.006%) and thyroid:brain weight ratio (control: 0.95%; borax: 0.73%) in males; increased brain:body weight ratio (borax) and liver:body weight ratio (boric acid) in females; a somewhat increased proportion of solid epithelial nests and minute follicles in the thyroid gland of borax-treated males; lymphoid infiltration and atrophy of the thyroid in boric acid treated females; increased width of the zona reticularis (borax males and females, boric acid females); and zona glomerulosa (boric acid females) in the adrenal gland.

37. 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.

38. **Chronic Oral Toxicity in SD Rats**: In the chronic study, Weir and Fisher (1972) fed Sprague-Dawley rats 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). The study was designed to assess systemic toxicity; only tissues

from the brain, pituitary, thyroid, lung, heart, liver, spleen, kidney, adrenal, pancreas, small and large intestine, urinary bladder, testes, ovary, bone, and bone marrow were examined histopathologically. Tumours were not mentioned in the report. There were 70 rats/sex in the control groups and 35/sex in the groups fed boron compounds. 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.

39. 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.

40. 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. Based on effects observed in the high-dose group, it appears that a maximum tolerated dose (MTD) was achieved in this study.

41. **Chronic Oral Toxicity in Beagle Dogs**: In the chronic toxicity study, 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.

42. 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." Tumours were not reported.

43. 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). New control dogs (4 males) were used for this follow up study. 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. The test animals had about an 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. Exposure was stopped at 38 weeks; at this time, one animal from each group was sacrificed and the remaining animal from each group was placed on the control diet for a 25-day recovery period prior to sacrifice.

44. 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. When the 2-year and 38-week dog studies are considered together, an overall 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.

45. **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. 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. 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.