Meeting

Annex A: Tabular summary of toxicity studies of boron

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

Study	Species / Route of exposure	Study details	Dose level	Findings	NOAEL or LOAEL

Heindel et al. (1992)	Timed pregnant Sprague Dawley Rats. Oral: Feed.	**Study duration:** Gestation Day (GD) 0-20. Additional group: GD 6-15. **No/Sex/Dose:** 26-28 per group.	**Original Dose:** 0, 0.1, 0.2 and 0.4% boric acid. Additional group: 0.8%. **Recalculated Dose Levels:** Rats: 0, 13.6, 28.5 or 57.7 mg B/kg bw/day. Additional group: 94.2 mg B/kg bw/day.	**Rats:** The average fetal body weight per litter was significantly reduced in a dose-related manner across all treated groups compared with the control group. At boron doses of 29 mg B/kg bw/day, there was a significant increase in the percentage of malformed fetuses per litter and the proportion of litters with at least one malformed fetus. Malformations consisted primarily of anomalies of the eyes, the central nervous system, the cardiovascular system and the axial skeleton. The most common malformations were enlargement of lateral ventricles in the brain and agenesis or shortening of rib XIII.	**Fetal LOAE** 13.6 mg B/k body weight day based o decreased b weight, incr fetal resorpt and malformatio **Fetal NOAE** Not found. **Maternal LOAEL**: 28.5 mg B/k body weight day. **Maternal NOAEL:** 13.6 mg B/k body weight day.

Price et al. (1996)	Sprague Dawley rats. Oral: Diet.	**Study duration:** Gestation Day (GD) 0-20. **No/Sex/Dose:** 60 per group.	**Original Dose:** 0, 0.025, 0.05, 0.075, 0.1 or 0.2 % Boric acid. **Recalculated Dose Levels:** 0, 3.3, 6.3, 9.6, 13.3 or 25 mg B/kg bw/day.	Fetal body weights were 99%, 98%, 97%, 94% and 88% of controls for the low- to high-dose groups, respectively. Incidences of short rib XIII (a malformation) or wavy rib (a variation) were increased in the 13.3 and 25 mg/kg body weight per day boron dose groups relative to control litters. There was a decreased incidence of rudimentary extra rib on lumbar 1 (a variation) in the high-dose group that was deemed biologically, but not statistically, significant.	**NOAEL:** 9.6 B /kg bw/da based on decreased f body weight

Weir and Fisher (1972)	Sprague-Dawley rats. Oral: Diet (Borax & Boric acid).	**Study duration:** 90-day sub chronic study. **No/Sex/Dose:** 10 males/group, 10 females/group.	**Original Dose:** 52.5, 175, 525, 1750 and 5250 ppm. **Recalculated Dose Levels:** 0, 2.6, 8.8, 26.3, 87.5 and 262.5 mg B/kg bw/day.	In animals receiving boron at a dose of 87.5 mg B/kg bw/day, body weights in males and females were reduced; absolute organ weights, including the liver, spleen, kidneys, brain, adrenals and ovaries, were also significantly decreased in this group. Organ to body weight ratios for the adrenals and kidneys were significantly increased, but relative weights of the liver and ovaries were decreased. A pronounced reduction in testicular weights in males in the 87.5 mg B/kg bw/day group was also observed.	**NOAEL:** 8.8 B/kg bw/day based on testicular atrophy.

Weir and Fisher (1972)	Beagle dogs. Oral: Diet (Borax & Boric acid).	**Study duration:** 90-day sub chronic study. **No/Sex/Dose:** 5 males/group, 5 females/group.	**Original Dose:** 17.5, 175 and 1750 and 5250 ppm **Recalculated Dose Levels:** Males: 0, 0.33, 3.9, 30.4 mg B/kg bw/day Females: 0, 0.24, 2.5 and 21.8 mg B/kg bw/day.	Testis weight was significantly lower than in controls in the middle- and high-dose groups (reduced by 25% and 40%, respectively). Testicular atrophy was observed in all of the dogs in the high-dose group but not in the other groups. In the borax study, testis weights were reduced compared with controls, but the reduction reached significance only in the high-dose group. All of the dogs in the high-dose group showed testicular atrophy. No other clinical or microscopic signs of toxicity were reported in any animals.	**NOAEL:** Males: 3.9 m B/kg bw/day based on testicular at and haemog destruction. Females: 2.5 B/kg bw/day

Weir and Fisher (1972)	Sprague-Dawley rats. Oral: Diet (Borax & Boric acid).	**Study duration:** 2-year chronic study. **No/Sex/Dose:** 35 males/group 35 females/group.	**Original Dose:** 117, 350 and 1170 ppm. **Recalculated Dose Levels:** 0, 5.9, 17.5 and 58.5 mg B/kg bw/day.	High-dose animals had coarse hair coats, scaly tails, hunched posture, swollen and desquamated pads of the paws, abnormally long toenails, shrunken scrotum, inflamed eyelids and bloody eye discharge. The haematocrit and haemoglobin levels were significantly lower, the absolute and relative weights of the testes were significantly lower, and relative weights of the brain and thyroid gland were higher than in controls. In animals in the middle- and low-dose groups, no significant effects on general appearance, behaviour, growth, food consumption, haematology, serum chemistry or histopathology were observed.	**NOAEL:** 17. B/kg bw/day based on testicular atrophy.

Weir and Fisher (1972)	Beagle dogs. Oral: Diet (Borax & Boric acid).	**Study duration:** 2-year chronic study. **No/Sex/Dose:** 4 males/group, 4 females/group. **Additional Study duration:** 38-week study with high dose. **No/Sex/Dose:** 4 males/group, 4 females/group.	**Original Dose:** 58, 117 and 350 ppm. High dose study: 0 & 1170 ppm. **Recalculated Dose Levels:** 0, 1.4, 2.9 and 8.8 mg B/kg bw/day. High dose study: 0 & 29.2 mg B/kg bw/day.	Testicular atrophy was observed in two test dogs receiving borax at 26 weeks and in the two dogs and one dog, respectively, killed after 26 or 38 weeks of boric acid consumption. The study was terminated at 38 weeks. The number of dogs was small and variable (one or two dogs at each of three time points) and inadequate to allow statistical analysis. All treated dogs at termination had widespread and marked atrophy in the seminiferous tubules, but testicular lesions also occurred in the control group.	**NOAEL:** 8.8 B/kg bw/day based on testicular at and spermatoge arrest. **LOAEL:** 29. B/kg bw/day

Weir and Fisher (1972)	Sprague-Dawley rats. Oral: Diet (Borax & Boric acid).	**Study duration:** Multigeneration study. **No/Sex/Dose:** 8 males and 16 females.	**Original Dose:** 0, 117, 350 or 1170 ppm. **Recalculated Dose Levels:** 0, 5.9, 17.5 or 58.5 mg B/kg bw/day.	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.	**LOAEL:** 58. B/kg bw/day **NOAEL:** 17. B/kg bw/day based on st and testicul atrophy.

Dixon et al. (1976)	Sprague-Dawley rats. Oral: Drinking water (Borax).	**Study duration:** Acute exposure: Single oral dose. **Subchronic exposure:** 90 days. **No/Sex/Dose:** 10 males/dose.	**Original Dose:** Acute exposure dose: - 0, 45, 150 and 450 mg/kg. Subchronic exposure dose: 0, 0.3, 1.0, and 6.0 mg B/L. **Recalculated Dose Levels:** Subchronic study: 0, 0.042, 0.14 and 0.84 mg B/kg bw/day.	No dominant lethal effects observed. No significant reproductive toxicity at tested doses. No changes in fertility, sperm production, or testicular histology. No significant changes in plasma FSH, LH, or testosterone after 90 days of treatment.	**NOAEL:** Acute toxici study: 450 mg/kg. Subchronic study: 0.84 B/kg bw/day

Lee et al. (1978)	Sprague-Dawley rats. Oral: Dietary exposure.	**Study duration:** 30 and 60 days. **No/Sex/Dose:** 18 male rats per group.	**Original Dose:** 0, 500, 1000, and 2000 ppm borax in food. **Recalculated Dose Levels:** 0, 2.8, 5.7 and 11.3 mg B/kg bw/day.	No significant adverse effects at 500 ppm. At 1000 and 2000 ppm, testicular atrophy, germ cell depletion, and reduced seminiferous tubular diameter observed. Increased plasma FSH levels; variable LH changes but no significant testosterone changes. 2000 ppm exposure led to persistent germinal aplasia and infertility even after 8 months of cessation.	**NOAEL:** 2.8 B/kg bw/day based on testicular atrophy.

Dixon et al. (1979)	Sprague-Dawley rats. Oral: Diet.	**Study duration:** 30 and 60 days (subchronic exposure). **No/Sex/Dose:** 18 males/dose.	**Original Dose:** 0, 500, 1000, 2000 ppm Borax. **Recalculated Dose Levels:** 0, 25, 50 and 100 mg B/kg bw/day.	Tubular diameter was significantly reduced in the 60-day treatment groups in all the doses. 500 ppm: No significant adverse effects. 1000 ppm: Significant loss of germinal elements, testicular atrophy, reduced spermatocytes and spermatogenic cells. 2000 ppm: Severe germinal aplasia, testicular atrophy, infertility, and irreversible damage in some cases. There was no dose-related decrease in litter size or fetal death in utero. Plasma FSH levels elevated at higher doses, but LH and testosterone remained unchanged. No dominant lethal effects observed. Testicular boron concentrations of 6-8 ppm associated with infertility.	**NOAEL**: 25 B/kg bw/day based on do related tubu germinal ap which was reversible a doses.

Seal and Weeth, (1980)	Long-Evans hooded rats. Oral: Drinking water.	**Study duration:** 70 days (starting at 28 days old). **No/Sex/Dose:** 15 males/group.	**Original Dose:** 0, 150, and 300 mg B/L (Borax). **Recalculated Dose Levels:** 0, 23.7 and 44.7 mg B/kg bw/day.	Rats consumed 150 mg B/L had 7.8% lower body weight, while those at 300 mg B/L had 19.8% lower body weight. High-dose group (300 mg B/L) showed atrophic scrotal sacs, coarse pelage, and long toenails. No significant kidney, liver, or adrenal weight differences were observed. Testes and seminal vesicle weights were significantly lower with boron exposure. Spermatogenesis was impaired at 300 mg B/L (only 3 out of 15 rats had spermatozoa). Plasma total protein and triglycerides were reduced at high doses. Bone calcium levels decreased at 300 mg B/L, suggesting possible interference with bone metabolism.	23.7 mg/kg bw/day base impaired spermatoge

Settimi et al. (1982)	2-months old Wistar rats. Oral: Drinking water.	**Study duration:** 3 to 14 weeks. **No/Sex/Dose:** 20 males/dose group.	**Original Dose:** 0 and 3 g/L sodium tetraborate. **Recalculated Dose Levels:** 0 and 20.8 mg B/kg bw/day.	Increased cerebral succinate dehydrogenase activity after 10 and 14 weeks. Increased RNA concentration and acid proteinase activity in the brain at 14 weeks. Decreased NADPH-cytochrome c reductase activity and cytochrome b5 content in the liver microsomal fraction after 10 and 14 weeks. Reduction in cytochrome P-450 concentration at 14 weeks. No significant change in body weight, liver, kidney, or testis weights compared to controls.	20.8 mg/kg/

Fail et al. (1991)	Swiss CD-1 mice. Oral: Feed.	**Study duration:** Reproductive assessment by Continuous Breeding Protocol (RACB) for both males and females; 27 weeks exposure of boric acid. **No/Sex/Dose:** **Task 2: -** 0 ppm: - 38 control pairs, 1000 ppm: 19 19 pairs, 4500 ppm: 20 pairs, 9000 ppm: 20 pairs. **Task 3: -** 1. 20 males from 4500 ppm + 20 control females, 2. 20 females from 4500 ppm + 20 control males, 3.19 control males + 19 control females	**Original Dose:** 0, 1000, 4500, 9000 ppm boric acid. **Recalculated Dose Levels:** 0, 19.2, 104.7 and 222.1 mg boron/kg bw/day for males. 0, 31.9, 148.1 and 290.5 mg boron/kg bw/day for females,	**Task 2: -** 1000 ppm had no significant effect on fertility. During 14 weeks of cohabitation, fertility was partially reduced at 4500 ppm and completely eliminated at 9000 ppm. Significant reduction in live litter size and body weight at 4500 ppm. 9000 ppm resulted in testicular atrophy, reduced sperm count and motility and increased abnormal sperm morphology. 4500 ppm males had lower reproductive organ weights and seminiferous tubule degeneration. Slight reduction in kidney/adrenal and liver weights in females at 4500 ppm. **Task 3: -** Males were the most affected sex, with reduced fertility at 4500 ppm	19.2 mg B/kg/day.

Harris et al. (1992)	Swiss CD-1 mice. Oral: Gavage.	**Study duration:** 1.Group A (Reproductive toxicity and Fertility assessment): Daily exposure for 19 days. 2.Group B (Pregnant and Developmental toxicity assessment): Gestational exposure (GD 8-14). **No/Sex/Dose:** **Males:** 10 per group. - **Females (Group A):** 10 per dose - **Females (Group B):** 10 pregnant per dose - **Litters:** Evaluated on Postnatal Days 0, 1, and 4.	**Original Dose:** 0, 120, 400, 1200 mg/kg/day boric acid. **Recalculated Dose Levels:** 0, 21, 70, 210 mg boron/kg bw/day.	**Reproductive Toxicity:** Significant testicular toxicity at 1200 mg/kg/day (exfoliation/disruption in >50% of tubules, with up to 50% germ cell loss in 7/9 mice receiving 1200 mg/kg/day for 19 days, testicular weight reduction). No effect on epididymal weight or sperm density. Increased post-implantation loss in gestationally exposed females at high doses. **Developmental Toxicity:** Reduction in live births at 1200 mg/kg/day. No neonatal mortality between PND 1 and PND 4.	21 mg B/kg bw/day base reduced tes weight and cell loss.

Ku et al. (1993)	Fischer 344 rats. Oral: Diet.	**Study duration:** 9-week exposure, recovery assessment up to 32 weeks post-treatment. **No/Sex/Dose:** 6 rats per group per week.	**Original Dose:** 0, 3000, 4500, 6000, and 9000 ppm boric acid (BA) in feed (corresponding to 545, 788, 1050, and 1575 ppm boron, respectively). **Recalculated Dose Levels:** 0, 26, 38, 52 or 68 mg B/kg bw/day.	3000 ppm: Mild inhibition of spermiation observed from week 5 onward. 4500 ppm: Severe inhibition of spermiation from week 2, leading to decreased epididymal sperm count (72-97% reduction). 6000 ppm: Severe inhibition of spermiation progressing to testicular atrophy by week 9. 9000 ppm: Testicular atrophy observed by week 6. No recovery from atrophy in the 9000-ppm dose even after 32 weeks post-treatment. Increased serum FSH and LH levels indicate a gonadotropin response to atrophy.	26 mg B/kg bw/day (LOA based on inhibition of spermiation

Chapin et al. (1997)	Fischer 344 rats (Male & Female). Oral: Diet.	**Study duration:** Study 1: 9 weeks Study 2: 12 weeks. **No/Sex/Dose:** Study 1: 6 males per dose level. Study 2: 6 males and 6 females per dose level.	**Original Dose:** Study 1: 3000, 4500, 6000, or 9000 ppm boric acid in diet. Study 2: 200, 1000, 3000, or 9000 ppm boric acid in diet. **Recalculated Dose Levels:** Study 1: 52.5, 78.8, 105 or 157.5 mg B/kg bw/day. Study 2: 3.5, 17.5, 52.5 or 157.5 mg B/kg bw/day. **Control diet contained 20-40 ppm boric acid**.	Serum phosphorous decreased in all boron-exposed groups. Serum magnesium reduced at all dose levels. Bone boron levels increased proportionally with dose, remaining elevated for up to 32 weeks post-exposure. Vertebral resistance to compression significantly increased at all dose levels (200 to 9000 ppm). No significant changes in tibia and femur resistance to bending. No histological changes in humerus bone structure.	3.5 mg B/kg bw/day.

Yoshizaki et al. (1999)	Wistar rats. Oral: Drinking water.	**Study duration:** 3 weeks. **No/Sex/Dose:** 20 males/group (treated); 10 females/group (untreated).	**Original Dose:** 50, 150, and 500 mg/kg/day Boric acid. **Recalculated Dose Levels:** 8.8, 26, 88 mg B/kg bw/day.	All parameters of epididymal sperm analysis were affected in males administered 500 mg boric acid/kg bw/day for 3 weeks and sperm number, motility, velocity and amplitude of lateral head displacement were also affected at 150 mg boric acid/kg bw/day. Morphological examinations revealed atrophy of seminiferous tubules and multinucleated giant cells in the testis in males administered 500 mg boric acid/kg bw/day.	8.8 mg B/kg bw/day.

Sabuncuoglu et al. (2006)	Albino Sprague-Dawley rats. Oral: Drinking water.	**Study duration:** 10, 30, and 45 days. **No/Sex/Dose:** 24/males/dose.	**Original Dose:** 0, 100, 275, and 400 mg/kg/day of boric acid. **Recalculated Dose Levels:** 0, 17.5, 48.1 and 70 mg B/kg bw/day.	Kidney weights, kidney boron concentration and histopathological changes were determined. Significant accumulation of boron in kidney tissue was seen in the experimental groups, but there was a significant drop in boron concentration on the 45th day compared with the 30th day. Histopathological degenerative changes were observed particularly in the proximal tubular cells and were dose and time dependent. The authors concluded that subacute boric acid exposure caused dose-dependent histopathological changes in kidney tissues of all dose groups.	17.5 mg B/k bw/day.