Summary of the Price et al. (1996) study

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19. 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”.

20. 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.

21. **Phase I Teratology Evaluation:** Phase I of this experiment was considered the teratology assessment and 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 show ed 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. In the high-dose group, gravid uterine weight was reduced by 10% compared to controls, which was statistically significant ($p<0.05$). The authors attributed this trend of reduced body weight and weight gain during late gestation to diminished gravid uterine weight. Corrected maternal weight gain (gestational weight gain minus gravid uterine weight) remained unaffected. Minimal decreases in maternal food intake were noted only in the high dose group and only during the first three days of dosing. 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.

22. **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. Additionally, a statistically significant trend ($p<0.05$) was identified for reductions in rudimentary extra ribs on lumbar I, a variation, although only the high-dose group showed a biologically relevant but not statistically significant decrease in this feature.

23. 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).

24. **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.

25. 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.

26. 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.

27. 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.