

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH**

SUMMARY OF TOXICOLOGY DATA

BORIC ACID, BIOBOR JF AND RELATED INORGANIC BORATES

BORIC ACID: Chemical Code # 769 Document Processing Number (DPN) # 50366 ¹
BIOBOR JF: 2,2-oxybis (4,4,6-trimethyl-1,3,2-dioxaborinane) [Chemical Code # 792] combined
with 2,2-(1-methyltrimethylenedioxy)bis-(4-methyl-1,3,2-dioxaborinane) [Chemical Code # 2227]

Document Processing Number (DPN) # 50439

Original date: August 26, 1987

Revisions: 7/10/89, 1/15/92, 7/24/92, 8/7/92, 1/20/95, Feb. 6, 2013, 8/26/13, 2/1/2016 and 9/18/17

DATA GAP STATUS

| | |
|--|---|
| Combined, rat: | No data gap, possible adverse effect indicated (not neoplasia) |
| Chronic toxicity, dog: | No data gap, inadequate studies on file, possible adverse effect; not required at this time |
| Oncogenicity, mice: | No data gap, possible adverse effect indicated (i.e., lifetime studies do not indicate neoplasia) |
| Reproduction, rat: | No data gap, possible adverse effect indicated ² |
| Reproduction, mouse: | No data gap, possible adverse effect |
| Developmental toxicity, rat: | No data gap, possible adverse effect |
| Developmental toxicity, rabbit: | No data gap, possible adverse effect ² |
| Teratology, rat: | No data gap, possible adverse effect |
| Teratology, rabbit: | No data gap, no adverse effect |
| Gene mutation: | No data gap, no adverse effect |
| Chromosome effects: | No data gap, no adverse effect |
| DNA damage: | No data gap, possible adverse effect |
| Neurotoxicity: | Hen neurotoxicity study is not required at this time. |

¹ Several inorganic borate active ingredients are listed below, with identifying numbers assigned by DPR for organizing data. For the purpose of filling data gaps, the following active ingredients have been grouped together: Boric acid (the lead chemical: Chemical Code 769; Tolerance # 50366),

Biobor JF (the lead chemical: Chemical Code 792, Tolerance # 50439), Boric oxide (Chemical Codes 5951 and 2090; Tolerance # 50683), Borax (Chemical Codes 70 and 5054; Tolerance # 50198), Sodium metaborate (Chemical Codes 689, 4012, and 4013); Tolerance # 50680), 792 (Chemical Codes 5053 and 1800; Tolerance # 50681), and Sodium tetraborate (pentahydrate) (Chemical Codes 79, 5054, and 1808; Tolerance # 50682). Studies pertaining to this Summary of Toxicological Data derived mainly from DPR Chemical Code # 769, with a few additional relevant studies limited to Chemical Codes 79 and 1800.

² Studies were conducted in more species than normally required for indicated study type. Toxicology one-liners are attached.

All record numbers for the above study types through 302552 (Document No. 50366-0235) were examined. Any record numbers > 900000 which exist (an older, discontinued numbering system), were also examined. Summary includes all relevant studies indexed by DPR as of September 22, 2017.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T170918

Previous Summaries by [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED] and [REDACTED]. Current summary is by [REDACTED] and [REDACTED].

NOTE: The following symbols may be used in the Table of Contents which follows:

** = data adequately address FIFRA requirement

† = study(ies) flagged as "possible adverse effect"

N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

No data have been provided at this time. Since test articles are inorganic anions, it is not clear what form such studies would take in any case.

SUBCHRONIC STUDIES (and subacute, if applicable) †

50366-047 959679 "90-Day Dietary Administration - Rats." (Hazleton Laboratories, VA, 12/12/62) Boric acid, 98.97 - 99.6%; fed in the diet to 10/sex/group at 0, 0.03, 0.1, 0.3, 1.0 or 3.0% of the diet (equivalent to 0, 0.00525, 0.0175, 0.0525, 0.175 and 0.525 nominal boron equivalent); all animals at 3% died before the end of the study; testicular atrophy in all males at 1.0% and 1/10 at 0.3%; ovaries and uterus showed no effect; body weights at 1.0% were -48% of controls for males -15% for females; supplementary data. No worksheet. (██████████, 7/7/89.)

50366-047 959680 "90-Day Dietary Feeding - Dogs." (Hazleton Laboratories, VA, 1/17/63) Boric acid, no purity stated; fed in the diet at 0, 100, 1000 or 10,000 ppm (equivalent to 17.5, 175 and 1750 ppm as elemental boron) to 5/sex/group; at 10,000 ppm (1.0%), all males showed severe atrophy of the testes with degeneration of the spermatogenic epithelium; changes in the adrenal glands at 1.0% in 3/5 females; testes weights lower in 1000 and 10,000 ppm group males; uterus not examined in females; supplementary data. No worksheet. (██████████, 7/7/89).

50681-005 067518 Weir, R. J., "90-day dietary administration - rats with 20 MULE TEAM BORAX (Sodium tetraborate decahydrate)." Hazleton Laboratories, Inc., Falls Church, VA, Feb. 15, 1963. Male Charles River Sprague-Dawley pathogen-free rats were dosed with 0, 154, 463, 1540, or 4630 ppm borax (10/group). After 13 weeks, testes were microscopically examined in all rats. There were no changes in body weights, clinical observations, or gross appearance of various organs, nor were there histological changes in the testes. Study is unacceptable (not designed to fill a data requirement), but provides useful data. No adverse effect is indicated. Aldous, 1/15/92. Note: this study was undertaken due to the unanticipated low LEL for testicular atrophy in an earlier study (record No. 067517, see below).

50681-005 067517 "90-Day Dietary Administration - Rats 20 MULE TEAM BORAX (Sodium tetraborate decahydrate)," (O. E. Paynter, Hazleton Laboratories Inc., December 13, 1962). Borax, purity assumed to be 100%, was administered in the feed at nominal concentrations of 0, 463, 1540, 4630, 15400, or 46300 ppm to 10 Sprague-Dawley rats/sex/group for 90 days. A "possible adverse effect" is indicated: testicular atrophy was observed in 10, 1, 0, and 4 males in the 15,400, 4,630, 1540, and 463 ppm groups, respectively. No NOEL was identified, due to the puzzling results, above. All 46,300 ppm rats died, as did one male at 15,400 ppm. The low dose testicular effect appears suspect, based on inconsistent effects in this study and lack of corresponding low dose effects in other subchronic and longer term rat studies. Study is not acceptable, due to numerous deviations from modern guidelines. (██████████ and ██████████, 1/15/92).

50681-005 067519 Paynter, O. E. "90-Day dietary feeding - Dogs: with 20 MULE TEAM BORAX (Sodium tetraborate decahydrate)." Hazleton Laboratories, Inc., 1/17/63. Five beagles per sex were dosed with 0, 0.0154, 0.154, or 1.54% borax in diet. Testicular atrophy was noted at 1.54% as the principal finding (no changes in testes were attributed to treatment at lower dosages). Small changes in morphology of adrenal cortex and in thyroids of females were noted at 0.154%. The testicular effects are "possible adverse effects," however this study is not pivotal, since lower NOEL's for testicular atrophy and/or changes in sperm quality have been noted in dog studies of longer duration, as noted in one-liners above. (██████████, 1/14/92 (no worksheet)).

****†50366-0232 281164**, "A 90-Day Oral (Gavage) Toxicity Study of Zinc Borate 2335 in Sprague Dawley Rats with a 28-Day Recovery Period"; 821; rat; WIL Research, 1407 George Road, Ashland, OH 44805-8946, Laboratory Project ID: WIL-946002, 6/21/99; Kirkpatrick, J.B.; Zinc borate 2335, Lot no. 10F01, > 98.8% pure, a white powder, was administered orally by gavage once daily for a minimum of 90 consecutive days to 4 groups (Groups 2-5) of CrI:CD(SD) rats. Dosage levels were 50, 100, 200, and 375 mg/kg/day for Groups 2, 3, 4, and 5, respectively. Groups 1 and 5 each consisted of 15 animals/sex and Groups 2-4 each consisted of 10 animals/sex. Following up to 92 days of dose administration, 10 rats/sex/group were euthanized; the remaining 5 rats/sex in the control and high-dose groups were euthanized following a 29-day non dosing (recovery) period. No mortality was reported. No treatment-related changes in body weight, bodyweight gains, food consumption, food efficiency, FOB, motor ability test, urinalysis in both sexes were observed. Serum chemistry examination revealed decreased cholesterol concentration in 100, 200 and 375 mg/kg/day group males, and in 200 and 375 mg/kg/day group females. Decreased triglycerides in mid/high dose group males were also observed. Decreased relative testes and epididymides weights at week 13 and 17 with decreased sperm mobility concentration, sperm morphological changes in high dose males at week 13 were observed. Reduced sperm motility and sperm concentration in the cauda epididymides were still reported at week 17 during recovery. Hyaline droplets in the glandular stomach were reported in both sexes at all dose levels. In the non-glandular stomach epithelial vacuolation and hyperplasia were observed in males at dose levels ≥ 200 mg/kg/day and in females at ≥ 100 mg/kg/day with incomplete recovery at week 17 at 375 mg/kg/day. Other histological changes including renal hypertrophy/vacuolation and pancreatic apoptosis in males at ≥ 100 mg/kg/day and females at 375 mg/kg/day were observed at week 13, but not present at week 17. Microscopic findings including kidney, pancreas, prostate and stomach in high dose groups males and females at week 13 and 17 were observed. NOEL (No Observed Effect Level): for male and female rats: 50 mg/kg/day based on histological changes in the pancreas, kidney and non-glandular stomach. Possible adverse effect. Acceptable (████ & █████, 6/15/2015).

CHRONIC STUDIES

Combined (Chronic and Oncogenicity), rat †

50366-078 088705 Draft protocol for combined rat study, dated 7/17/90. CDFA review of 8/14/90 noted that the protocol appeared to be appropriate. A few comments were made by CDFA reviewer, █████

50366-048 959678, "Two-year Dietary Administration - Albino Rats, Boric Acid, Final Report." (Hazleton Laboratories, Inc., Falls Church, VA, # 182-104, 7/8/66). Boric acid, 98.69% - 100.02%, was fed in the diet for 2 years at 0, 670, 2000, or 6700 ppm (equivalent to 117, 350 and 1170 ppm elemental boron); 35 rats/sex/level with 70/sex for controls. Interim sacrifices of 5/sex/dose at 6 and 12 months. No ophthalmology. Nominal NOEL = 2000 ppm (0.20%), based on the following adverse effects: decreased b.w. (-19% in males and -28% in females at termination), reduced hemoglobin, atrophic testes in all high dose males at 6, 12 and 24 month sacrifices, lower liver weight and lack of ovulation, discharge from eyes with eyelid gland changes. UNACCEPTABLE, not upgradeable (too few animals for an oncogenicity study, inadequate histopathology with only 10/sex/dose at term although more survived, limited sampling for diet analysis and results not reported, no eyes for histopathology and no ophthalmology). (████, 6/27/85 and 6/26/89).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/7/89) notes EPA classification as "minimum."

50366-048 035663 Addendum to 048 959678 - Boron content of tissues.

50198-010 038963, "Two-year Dietary Administration-Albino Rats." (Hazleton Laboratories America Incorporated, HLA Study No.182-104, July 8, 1966). Borax (sodium tetraborate decahydrate, 104 % theoretical boron content) was administered in the diet at 0, 0.103, 0.308 or 1.03 % (equivalent to 117, 350 or 1170 ppm of elemental boron) of 35/sex/dose in the test group and 70/ sex in the control group. At 6 and 12 months, 5 rat/sex/group were sacrificed and at the termination of the study all the surviving animals from control and test groups were sacrificed. Mean body weight/weight gain were reduced in males; (-9 to -16 % below controls) in 0.308 % and 1.03 % test groups, in females; (-9 to -33 % below control) in all test groups. Survival at 104 weeks was comparable among the test groups and the controls. Hematological values (cell volume and hemoglobin) for both the sexes at 0.103% and 0.308% were within normal limits, at 1.03%, were below or within the low normal range when compared to the controls at time intervals 2, 3, 6, 12, 18 and 24 months. There were no treatment-related effects on biochemical and urinalysis parameters. The testes weights and testes/body weight ratios of males at 1.03 % were significantly lower than those for controls. Testicular tubular atrophy and decrease tubular size was found in all males of 1.03 % group sacrificed at 6, 12 or 24 month interval. The NOEL is 0.103 % (decreased body weight gain) and NOAEL is 0.308 % (testicular atrophy). Possible adverse effect. Study upgraded to acceptable [REDACTED] 6/22/89; upgraded, [REDACTED] and [REDACTED], 9/29/2017).

50681-006 068030 duplicate of 50198-010 038963.

50366-051 035659, "The Toxicity of Boric Acid and Sodium Tetraborate: A Literature Review," (U.S. Borax Research Corp., Griffin, T.S., 8/29/78). References include Weir, R. J. Jr., and Fisher, R. S., 1972, Toxicologic Studies on Borax and Boric Acid; Toxicol. and Appl. Pharmacol. 23: 351," which summarizes information in 048 959678. UNACCEPTABLE (summary information only). ([REDACTED] 8/11/87)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/7/89) notes EPA classification as "supplementary."

Summary: It is recognized that the above studies are deficient in providing data on individual body weights, food consumption, ophthalmological examinations, some clinical parameters and histopathology. However, the study was designed and conducted prior to EPA's GLP guidelines; hence the study is acceptable and provides sufficient information for an acceptable combined rat chronic toxicity /carcinogenicity study (Boric acid/Sodium salts of Boric acid. Human Health Draft Risk Assessment for Registration Review; Mathew Crowley, Linnea J.Hansen, Dennis McNeilly, USEPA Dec 1, 2015).

Chronic, dog †

50366-078 088706 Draft protocol for chronic dog study, dated 7/17/90. CDFA review of 8/14/90 noted that protocol appeared to be appropriate. A few comments were made by CDFA reviewer, [REDACTED].

50366-047 959663, "38-Week Dietary Feeding - Dogs, Boric Acid, Final Report," (Hazleton Laboratories, Inc., Falls Church, VA., 2/28/67), boric acid > 99.94% purity, fed in the diet for 38 weeks at 0 or 6700 ppm (equivalent to 1170 ppm elemental boron); 4 beagle dogs/sex with 2/sex necropsied at 26 weeks. Hematology, clinical chemistry and urinalysis at several intervals with basic parameters measured. No ophthalmology and no eye tissues for histological examination. No evidence of boron accumulation in selected tissues. NOEL < 6700 ppm, based on testicular atrophy (seen at 26 weeks and 38 weeks) and inactive ovaries. UNACCEPTABLE, not upgradeable (only 38 weeks, only 1 dose level). ([REDACTED] ([REDACTED]) 6/26/85 and 6/26/89)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/7/89) notes EPA classification as “supplementary.”

50681-005 067520 Weir, R. J., “38-week dietary feeding - dogs: Borax (sodium tetraborate decahydrate),” Hazleton Laboratories, Inc., 2/28/67. Four beagles per sex were given control or 1.03% borax in diet. Two/sex/group were sacrificed at wk 26. The other two controls/sex and one treated dog/sex were sacrificed at wk 38. The remaining dog/sex on treatment was placed on control diet for 25 days prior to sacrifice. “Testicular atrophy and spermatogenic arrest” were attributed to treatment, a “possible adverse effect.” Investigators described the male recovery study dog as having a “moderate degree of degeneration and evidence of complete cessation of spermatogenesis.” Varying degrees of testicular degeneration or atrophy in controls confounded interpretation, however investigators considered that testicular atrophy was a probable treatment effect. Study is not acceptable, and not upgradeable (no NOEL identified, only one dose level, too few animals under any given dosing regimen, too few tissues examined, no ophthalmology), but provides useful information. [REDACTED], 12/04/91.

50198-011 038964 “Two-Year Dietary Feeding - Dogs Borax (sodium tetraborate decahydrate) Final Report.” (Hazleton Laboratories, VA, 7/8/66, Project No. 182-106) Borax, average of 104% theoretical boron content, fed to beagle dogs at 0, 0.051, 0.103 or 0.309% (equivalent to 59, 117 and 350 ppm as elemental boron) of the diet for 1 or 2 years; 4/sex/dose; 1/sex/dose sacrificed after 1 year, 2 - 3/sex/dose after 2 years with 1/sex in control and high dose fed control diet for 3 months after 2 years for a recovery study; boron levels in blood, urine, feces and selected tissues measured at several intervals; possible adverse effects on sperm motility and count at 0.309%; NOEL/NOAEL cannot be determined since sperm viability was not measured at 0.51 and 0.103%; unacceptable (inadequate tissues for histology, no ophthalmology, no analysis of diet, no NOEL determined) [REDACTED], 6/23/89.

50681-007 068031 Duplicate of 50198-011 038964.

50366-049 959677 “Two-Year Dietary Feeding -Dogs, Boric Acid, Final Report,” (Hazleton Laboratories, Inc., Falls Church, VA., # 182-106, 7/8/66), Boric Acid > 98.6% purity, fed in the diet for 2 years at 0, 330, 670, or 2000 ppm (equivalent to 58, 117 and 350 ppm as elemental boron); 4 beagle dogs/sex/level (1/sex/level sacrificed at 1 yr). NOEL = 670 ppm based on the following adverse effects seen at 2000 ppm: slight microscopic changes in testes and increased epithelial nests in thyroid. UNACCEPTABLE, not upgradeable (no toxicity at high dose, no ophthalmology, no analysis of diet for content of boron, limited list of tissues for histopathology). [REDACTED] [REDACTED] 6/27/85 and 6/26/89)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/7/89) notes EPA classification as “minimum.”

50366-049 035664, Addendum to 049 959677

50366-051 035659, “The Toxicity of Boric Acid and Sodium Tetraborate: A Literature Review,” (U.S. Borax Research Corp., Griffin, T.S., 8/29/78). References include Weir, R. J. Jr., and Fisher, R.S., 1972, Toxicologic Studies on Borax and Boric Acid; Toxicol. and Appl. Pharmacol. 23: 351 which summarizes information in 049 959677. UNACCEPTABLE (summary information only). [REDACTED] 8/11/87)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/7/89) notes EPA classification as “supplementary.”

Oncogenicity, mouse ** †

** **50366-070 065131** “Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F1 Mice (Feed Studies).” (EG&G Mason Research Institute for NTP, October, 1987, Technical Report Series, No.

324) Boric acid, 99.7%; fed to B6C3F1 mice, 50/group, at 0 (diet), 2500 or 5000 ppm for 103 weeks; NOEL < 2500 ppm (decreased weight gain and survival), NOAEL = 2500 ppm (testicular atrophy and interstitial cell hyperplasia at 5000 ppm); ACCEPTABLE with a possible adverse effect. ([REDACTED], 6/21/89).

50366-068 065464 Exact duplicate of 065131 (from another registrant).

50366-067 075634 Exact duplicate of 065131.

50366-071 067243 Exact duplicate of 065131 (deleted from system).

50366-0235 302548 "Toxicity and Carcinogenicity Studies of Boric Acid in Male and Female B6C3F1 Mice." Micheael P. Dieter. National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. Environ Health Perspect 102 (Suppl 7): 93-97 (1994). Both male and female B6C3F1 mice were given diets with boric acid for 14 days, 13 weeks or 2 years. Dietary doses used in the acute, 14 day study were 0, 0.62, 1.25, 2.5, 5 and 10%; in the subchronic 13-week study were 0, 0.12, 0.25, 0.50, 1 and 2 % and doses in the 2 year chronic study were 0, 0.25 and 0.50% in the diet. In the 14 day study, mortality in male mice was 1/5, 3/5 and 5/5 day ingesting 2.5, 5 and 10 % of boric acid, respectively observed as early as day 7; mortality in 4/5 female mice at 10% boric acid between days 9 and 11. Body weights decreased more than 10% below controls in the higher dose groups of both sexes. In the 13-week study, 8/10 males and 6/10 females fed with 2 % boric acid dies between weeks 1 and 88; one male mouse of 1 % dose group died at week 2 of exposure. Body weight decreased from 10 to 23 % below those of controls occurred in males fed 0.5, 1.0 and 2 % boric acid and of 8 to 18% in the female mice from the same group. Minimal to mild extramedullary hematopoiesis in spleens of both sexes was a common occurrence in all dose groups. Severe testicular degeneration or atrophy of the seminiferous tubules was observed in male mice fed 0.5 to 2.0% boric acid. In the 2 year study, dietary doses of 0.25% and 0.50% were selected for both sexes of mice based on body weights and mortality. Survival in male mice was reduced in the high dose group after week 63 and after week 84 in the low dose group. Survival in female mice was not affected at either doses of boric acid. Body weight gain was reduced in the high dose group of both sexes. Increased incidence of testicular atrophy (3/49, 6/50, 27/47) and interstitial cell hyperplasia (0/49, 0/59, 7/47) was noted in control, low and high dose male mice, respectively. There was slight increase in spleen lymphoid deletion in dosed male mice which was considered secondary to stress and debilitation. The combined incidence of hepatocellular adenomas or carcinomas were 14/50, 19/50 and 15/49 in the male mice fed with 0, 0.25 and 0.50 % boric acid, respectively for 2 years. The combined incidences of sarcomas, fibrosarcomas or neurofibrosarcomas in the same-dose group of mice were 2/50, 10/50 and 2/50. Although there was an increase in the subcutaneous tissue tumors and hepatic tumors in dosed male mice, these fell within the historical control range and were believed to be not related to chemical treatment. These particular tumors are highly variable in historical controls, only occurred in the low dose group and were not significant by an incidental tumor test which is appropriate for tumors that are not the cause of death. None of these tumors or any other kind were increased in female mice. Mutagenicity assays with *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were negative in the presence or absence of S9 fractions prepared from livers of Aroclor 1254-induced male Sprague-Dawley rats or Syrian hamsters. Tests in the mouse lymphoma L5178Y/TK +/- assay with or without activation by S9 from Aroclor 1254-induced male F344 rat liver were negative. There were no effects on sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells indicating that boric acid is not genotoxic. **Summary report.** ([REDACTED] 9/20/17)

GENOTOXICITY

Gene mutation **

50366-051 35658, Griffin, T.S., 1978. The Toxicology of Boric Acid and Sodium Tetraborate: A Literature Review. (U.S. Borax Research Corp., Griffin, T.S., 8/29/78). Includes 2 references to articles related to mutagenic effects in bacteria. The first reported an increase in back-mutation to streptomycin dependence (Demerec et al., 1951), but the second, considered by Griffin to be more sensitive, reported no significant mutagenic activity (Iyer and Szybalski, 1958). UNACCEPTABLE (summary information only). [REDACTED] 8/11/87)

50366-070 065131 "Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F1 Mice (Feeding Studies)." (EG&G Mason Research Institute, October, 1987, NTP Report No. 324) Boric acid, 99.7%. This report briefly described a bacterial reverse mutation study using *Salmonella typhimurium*, strains TA1535, TA1537, TA98 and TA100, at 0 (vehicle not stated), 33, 100, 333, 1000 or 1820 µg/plate, 20 minute incubation before adding agar and plating; with and without male Sprague-Dawley rat liver and Syrian hamster liver Aroclor 1254-induced S9 fraction; triplicate plates, two trials; data from one trial only as mean + standard error; both trials stated to give similar results; single page report in Appendix C (page 88) of this report; inadequate information - full report should be submitted; UNACCEPTABLE but no evidence of an adverse effect. Possibly upgradeable. [REDACTED], 6/21/89).

50366-070 065131 "Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F1 Mice (Feed Studies)." (EG&G Mason Research Institute, October, 1987, NTP Report 324) Boric acid, 99.7% technical grade; tested with mouse lymphoma cells with and without S9 from Fischer 344 male rats, induced with Aroclor 1254; incubated for 4 hours with boric acid followed by a 48 hour expression time; concentrations of 0 (vehicle not stated), 1000, 1800, 2600, 3400, 4200 or 5000 µg/ml without S9 and 0, 1000, 2000, 3000, 4000 or 5000 µg/ml with S9; duplicate cultures; two trials with data from one trial reported and statement that both trials gave similar results; two pages only in appendix C of oncogenicity study; TFT to select mutants; UNACCEPTABLE with inadequate reporting of study but possibly upgradeable with submission of a full report and results of both trials for evaluation; no evidence of an adverse effect. [REDACTED], 6/21/89).

** 50366-080 098306 "Salmonella/Microsome Plate Incorporation Assay of Boric Acid." (K. R. Stewart, SRI International, Study No. 2389-A200-91, 8/12/91) Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to boric acid in the plate incorporation assay without S9 or with 4% or 10% Aroclor 1254-induced male rat liver activation. Concentrations were 0, 10, 50, 100, 500, 1000 or 2500 µg/plate. Two assays with triplicate plates in each. No evidence of cytotoxicity at any concentration. Boric acid was soluble in water at 50 mg/ml (= 2500 µg/plate). No increase in revertants. Negative for an adverse effect. Acceptable. [REDACTED], 12/9/91.

** 50366-080 098307 "Mouse Lymphoma Cell Mutagenesis Assay (tk+/- / tk-/-) of Boric Acid." C. J. Rudd, SRI International, Study No. 2389-G300-91, 8/23/91). Boric acid, granular technical, >99% purity, was exposed to mouse lymphoma L5178Y cells for 4 hours with and without male rat liver S9 activation. Concentrations were 0 (medium), 1.2, 1.7, 2.45, 3.5 or 5 mg/ml. There were duplicate cultures and two independent trials. Positive controls were hycanthone methane sulfonate and 3-methylcholanthrene, both functional. There was no indication of a reproducible increase in mutation frequency. Acceptable. [REDACTED], 12/10/91.

Chromosome damage **

50366-070 065131 "Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F1 Mice (Feed Studies)." (EG&G Mason Research Institute, October 1987, Report No. 324). Technical boric acid, 99.7%; tested with Chinese hamster ovary cells with and without S9 from Aroclor 1254 induced male Sprague-Dawley rat liver; incubated without S9 for 8-10 hours at 0 (DMSO), 500, 1000, 1500 or 2000

µg/ml followed by 2-3 hours with colcemid; with S9 at 1000, 1600, 2000 or 2500 µg/ml, for 2 hours followed by an additional 8 - 10 hours incubation including 2-3 with colcemid; harvested by mitotic shake-off; scored 100 cells per concentration; positive controls of mitomycin C (-S9) and cyclophosphamide (+S9); no evidence of an adverse genotoxic effect; summary table only, page 91 of mouse oncogenicity study; UNACCEPTABLE with inadequate information - full study should be submitted for evaluation. (█████, 6/21/89).

** 50366-080 098309 "Bone Marrow Erythrocyte Micronucleus Assay of Boric Acid in Swiss-Webster Mice." (K. G. O'Loughlin, SRI International, Study No. 2389-C400-91, 8/19/91) Boric acid, granular technical, > 99% purity, was given on two consecutive days at 0 (water), 900, 1800 or 3500 mg/kg/day to 10/sex/group. Doses were based on 1) a range-finding study and 2) the stated maximum practical dose. Five/sex/group was sacrificed at 24 and at 48 hours. Bone marrow from each animal was assessed for % PCE/RBC and % PCE with micronuclei. Urethane was given as a positive control to male mice and was functional. No evidence for induction of micronuclei formation in the bone marrow (or peripheral blood in the range-finding study). Although there some differences from current suggested protocol, the study is acceptable with no adverse effect. (█████, 12/10/91).

DNA damage or miscellaneous effects ** †

50366-070 065131 "Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F1 Mice (Feed Studies)." (EG&G Mason Research Institute, October, 1987, Report No. 324 of NTP). Sister chromatid exchange assay. Technical boric acid, 99.7%; tested with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9; without S9 at 0 (medium and DMSO), 200, 300, 400 or 500 µg/ml, 22-24 hours with BrdU added after 2 hours at 10 mM and colcemid for 2-3 hours; with S9, at 0 (medium and DMSO), 250, 500, 1600 and 2000 µg/ml, 2 hours followed by washing and an addition 26 hours including BrdU and colcemid; no justification of concentrations and no reporting of whether cytotoxicity was seen; no evidence of increase in sister-chromatid exchange; no indication of the number of cells scored; UNACCEPTABLE - inadequate reporting with a single summary table on page 91 of mouse oncogenicity report. Full study should be submitted for evaluation. (█████, 6/21/89).

** **50366-080, 086 098308, 115317** "Evaluation of the Potential of Boric Acid to Induce Unscheduled DNA Synthesis in *in vitro* Hepatocyte DNA Repair Assay Using the Male F-344 Rat." (J. P. Bakke, SRI International, Study No. 2389-V500-91, 8/23/91, amendment 5/20/92) Boric acid, granular technical, >99% purity, was tested with primary hepatocytes from male F-344 rats, three cultures per concentration for 19 hours. Unscheduled DNA synthesis was measured by autoradiography. Concentrations in the first trial were 0 (medium), 10, 100, 250, 500, 1000 or 5000 µg/ml. In the second trial, concentrations were 0, 5, 10, 50, 100, 250, 500, 1000, 2500, 3800 or 5000 µg/ml. Thirty cells per slide for a total of 90 were scored per concentration. Data presented as summary only. Insufficient information for evaluation of a possible adverse effect. Initially evaluated as unacceptable, possibly upgradeable with submission of individual scores and toxicity information. (█████, 12/10/91). Submission of 115317 upgrades the study to acceptable status. Examination of the data for the 3 slides per concentration suggests a possible adverse effect with an increase in the nuclear grains but especially in the % in repair. (█████, 8/7/92).

50366-086 115317 Addendum to 098308. Contains the cytotoxicity information and the individual data for the slides scored. (█████, 8/7/92).

A rebuttal on the above study was submitted by the registrant objecting to the finding of a possible adverse effect in 098308. The document has been reviewed and considered. There is no change in status - the study remains acceptable with a possible adverse effect. (█████, 1/12/95).

REPRODUCTIVE TOXICITY, RAT †

Note: The most recent reproduction data are in the mouse (see separate section below).

50198-012 038965 "Three-Generation Reproduction Study - Rats; Borax (Sodium Tetraborate Decahydrate) - Final Report." (Hazleton Laboratories, VA, 7/8/66, project no. 182-105) Borax, no purity stated; fed in the diet to rats at 0, 0.103, 0.308 or 1.03% (equivalent to 117, 350 and 1170 ppm elemental boron), 8 males and 16 females per group; three generations, 2 litters per generation for low and mid doses; complete infertility at 1.03% - possible adverse effect (testicular atrophy and lack of viable sperm, decreased ovulation, infertility at nominal 1.03%); NOAEL (nominal) = 0.308% based on reproductive effects and clinical signs in adults. Unacceptable but possibly upgradeable (no diet analysis, no histopathology on F1 and F2 adult breeders at low and mid dose although tissues were saved, no purity of borax, no individual data). [REDACTED], 6/23/89.

50681-008 068032 Duplicate of 50198-012 038965.

50366-049 959681, "Three-Generation Reproduction Study - Rats, Boric Acid, Final Report," (Hazleton Laboratories, Inc., Falls Church, VA., # 182-105, 7/8/66) Boric acid > 98.69% purity, fed in the diet for 3 generations, 3 litters/generation at 0, 670, 2000, and 6700 ppm, 8 males and 16 females per group. Apparent NOEL = 2000 ppm, based on the following adverse effects seen at 6700 ppm: general (decreased body weight, poor appearance) and reproductive (small, soft testes; congested or cystic ovaries; no conceptions). High dose females were mated with control males - 1 litter and 3 abortions; UNACCEPTABLE, (no histopathology on F1 parents although tissues were taken; no analysis of diet, husbandry problems, no individual data). Possibly upgradeable with submission of missing data. ([REDACTED] [REDACTED]) 6/27/85 and 7/7/89).

50366-051 035660, "The Toxicity of Boric Acid and Sodium Tetraborate: A Literature Review," (U.S. Borax Research Corp., Griffin, T. S., 8/29/78) Includes 3 references to articles related to reproductive effects. The first article reports no effects on fertility in rats given single oral doses of 45, 150, or 450 mg/kg as boron, and no reproductive effects of changes in serum chemistry, body, testis, seminal vesicle or prostate weights in rats exposed to drinking water containing 0.3, 1, or 6 mg/l boron (1 mg boric acid = 0.175 mg boron). Another study reported gonadotropic effects at a drinking water concentration of 6 mg/l. A third study reported decreased b.w. gain, and smaller testes or ovaries after 7 weeks at 300 mg/l drinking water, with a NOEC of 75 to 150 mg/l. UNACCEPTABLE (summary information only). ([REDACTED]), 8/11/87).

50366-0235 302551 "Effect of Acute Exposure to Boric acid on the Male reproductive System of the Rat." Ralph E. Linder, Lillian F. Strader, Georgia L. Rehnberg; Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina; Journal of Toxicology and Environmental Health, 31:133-146, 1990. In a time-response study, four groups (6/group) male Sprague-Dawley rats were dosed orally on day 0 with 0 or 2000 mg/kg of boric acid and sacrificed on posttreatment day 2, 14, 28 and 57. In a dose-response study, 8 male rats per dosage group were dosed with 0, 250, 500, 1000 or 2000 mg/kg of boric acid and sacrificed on posttreatment day 14. The animals were given oral doses of either water or boric acid solution (5% in water) was administered in a dose volume of 20ml/kg. In the time-response study the animals were killed under ether anesthesia by severing the abdominal aorta. In dose-response study the unanaesthetized animals were decapitated and blood was collected for serum hormone assays for lutenizing hormone, follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH) and prolactin (PrI) by double-antibody radioimmunoassay. The testes, epididymides, prostate and seminal vesicles were excised, weighed and processed for light microscopy. The contralateral testis was frozen for sonication-resistant sperm head counts. The contralateral epididymis was used for determination of cauda sperm motility, caput and cauda sperm morphology and caput and cauda sperm reserves. For the sperm motility assay, approximately, 2.5 mg (time response study, day 2 and 14) or 5.0 mg (all other animals) of cauda luminal fluid was collected. For all other animals, the percentage of motile spermatozoa and the straight-line swimming velocities were determined by videomicrography. In the time-response study,

no clinical signs of toxicity were observed in rats at 2000 mg/kg of boric acid. Boric acid affected spermiation, caput sperm reserves and epididymal sperm morphology after acute exposure to 1000 or 2000 mg/kg. Testicular effects were indicated by abnormal retention of Step 19 spermatids at 2000 mg/kg boric acid on day 14. Serum LH, FSH, TSH and prolactin values were not affected at any dosage. By 57 days posttreatment, epididymal sperm parameters were recovered indicating that the effects were reversible at the dosage levels tested. No adverse effect indicated. No-observed effect level was 500 mg/kg. **Summary report.** (██████████ 9/17/17)

REPRODUCTIVE TOXICITY, MOUSE †

(Following is a supplementary study in a second species for this study type)

50366-081 098310 Fail, P. A., George, J. D., Grizzle, T. B., Heindel, J. J., and Chapin, R. E., "Final report on the reproductive toxicity of boric acid (CAS No. 10043-35-3) in CD-1 Swiss mice." Research Triangle Institute, 4/13/90. NTP Report #90-105. COBS CrI:CD-1® (ICR)BR VF/Plus™ outbred Swiss mice were placed in a continuous breeding program for 98 days. There were forty pairs of controls and 20 pairs each at doses of 1000, 4500, and 9000 ppm boric acid (98-99%) in diet. The last litters from the original F0 pairings provided F1 parents. The F1 parents were limited to control and 1000 ppm groups, due to total infertility (9000 ppm group) or very poor fertility (4500 ppm group). Selected F1 pups were maintained for 74 + days on dose, then mated within dose groups for up to 7 days. These animals were necropsied at weaning of a single litter per pair. Meanwhile, a crossover study was performed, in which F0 adults, having completed the continuous breeding study, were taken off treatment for one week, then mated as: control males X control females, 4500 ppm males X control females, or 4500 ppm females X control males. The analysis of crossover study offspring was limited to fertility, litter size, and litter survival. Surviving F0 adults (except 1000 and 9000 ppm females) and F1 parents were necropsied and at least major reproductive organs were microscopically examined. NOEL = 1000 ppm (possible adverse effects: markedly reduced fertility, reduced litter sizes, increased % of pups born dead, smaller pup weights, apparent reduction in pup survival, germinal epithelium of males was markedly degenerated or atrophied, with hypospermia or aspermia, sperm were reduced in concentration and motility, and sperm abnormalities were increased). In the crossover study, females from the 4500 ppm group mated to controls had normal mating and fertility indices, and normal live litter sizes. In contract males previously treated at 4500 ppm group mated to controls had only 6 of 20 males which mated, of which only one yielded a litter. That one litter had only 3 pups. Adult effects included marked increase in water consumption at 4500 ppm and above. This was evidently designed as a supplemental study, not designed to fill a data requirement, and provided useful information. ██████████, 1/6/92, with clarifications of this 1-liner by ██████████ on Feb. 6, 2013.

50366-079 091186 and 091187 Exact duplicate of 081:098310.

50366-0235 302552 "Reproductive Toxicity of Boric Acid in Swiss (CD-1) Mice: Assessment Using the Continuous Breeding Protocol." Patricia A. Fail, Julia D. George, John Cutisseely, Thomas B. Grizzle and Jerrold J. Heindel. Research Triangle Institute, Research Triangle Park, North Carolina; PATHCO, Incorporated, Research Triangle Park, North Carolina; Developmental and Reproductive Toxicology Group, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. *Fundamental and Applied Toxicology*, 17, 225-239 (1991). The potential reproductive toxicology of boric acid (BORA) in CD-1 Swiss mice was evaluated using the Reproductive Assessment by Continuous Breeding (RACB) Protocol. Bora was administered in the feed for 27 weeks to males and female mice at concentrations of 0, 1000, 4500, or 9000 ppm. For the F1 generation, only 0 and 1000 ppm doses were administered due to reduced fertility in the F0 generation at the higher doses. During 14 weeks of cohabitation, the mid-dose of 4500 ppm of BORA

caused significant decrease in all parameters of reproductive performance; the average numbers of litters per pair, live pups per litter, proportion of pups born alive, the live pup weight and adjusted live pup weight. Fertility of F0 mice was totally impaired at 9000 ppm. No litters dead or alive were produced by 9000 ppm cohabited pairs. Feed consumption increased in 9000 ppm group after 5 weeks and in 4500 ppm group by week 13. Water consumptions significantly increased in 4500 and 9000 ppm group pairs. Lack of gain in body weight of high-dose group animals implied generalized toxicity and indicated 9000 ppm as maximally tolerated dose (MTD). At necropsy, after 27 weeks of BORA exposure, F0 males in 9000 ppm group had reduced body and reproductive organ weights, increased incidence of abnormal sperm, decreased sperm concentration and motility, and seminiferous tubule degeneration. Significant decreased weights of kidney/adrenal glands and livers in the females; significant decreased weights of kidney/adrenal glands in the males of 4500 ppm group were observed. A crossover mating trial of control and 4500 ppm groups confirmed the male as the affected sex; with fertility rates and mating index significantly lower in the 4500 ppm male X 0 ppm female group but not in the 4500 ppm female X 0 ppm male when compared to 0 ppm male X 0 ppm female group. At 4500 ppm, (F1 pups only), decreased mean pup weight and reductions in the number of live pups per litter, and number of pups born alive were observed. **Parental NOAEL:** 1000 ppm (based on body and reproductive organ weights measured). **Offspring NOAEL:** 1000 ppm (based on reduced pup weight and decreased live pups at birth). The last litters of the control and 1000 ppm females born in the 14 week breeding phase were reared to 74 days of age and then mated in nonsibling pairs within treatment groups. These F1 mice had normal fertility but the adjusted mean body weights of F2 pups were significantly decreased when compared to the controls. These data establish the reproductive toxicity of BORA in CD-1 mice and demonstrate that the male is the most sensitive sex. **Summary report.** (██████████, 9/17/17)

REPRODUCTIVE TOXICITY, HUMAN †

50366-0235 302549 "Chronic Boron Exposure and Human Semen Parameters." Wendie A. Robbins, Lin Xun, Juan Jia, Nola Kennedy, David A. Elashoff, Liu Ping. Center for Occupational and Environmental Health, University of California, Los Angeles, USA; School of Nursing, University of California, Los Angeles, USA; Biostatistics Department School of Public Health, University of California, Los Angeles, USA; Environmental health sciences department, School of Public health, university of California, Los Angeles, USA; Chinese Society for Environmental Sciences Beijing, China. *Reproductive Toxicology* 29 (2010) 184-190. The study involved male workers (n=74) at boron mining and processing plant of ages 18-40 years and comparison groups of men not working in the boron industry in Kuandian County, PR China. Two comparison groups were enrolled; one control group (n=70) was from a region with very little boron in ground water and soil; another group (n=63) referred to as community comparison group was assessed for the effects of environmental exposure to boron through food and water due to living in the area of boron industry with high environmental boron but not working in the boron industry. Interview data was collected based on work, general health, reproductive health, diet and life style using a 51 item questionnaire guide. A composite of total daily exposure was generated by adding exposure through workplace inhalable dust, food and fluid intake. Post-workshift urine was used to predict total exposure for the study groups. Biologic markers of boron dose were measured in blood, urine and semen. Exposure was calculated in terms of elemental boron. Dust, dietary intakes of food and fluids were analyzed by ICP-AES (Inductively Coupled Plasma-Atomic Emission Spectrometry) and biologic samples were analyzed by ICP-MS (Inductively Coupled Plasma-Mass Spectrometry). Semen samples were collected to determine the correlations between semen parameters including total sperm count, sperm concentration, motility, morphology, DNA breakage, apoptosis and aneuploidy. Based on the interview data, the three comparison groups did not differ significantly on general health status, history of infertility, having a prior semen analysis, history of radiation or surgery or injury to the genital track, exposure to other known reproductive toxicants, use of contraception, years of marriage, spontaneous pregnancy loss, still births or birth defects in offspring. Blood boron averaged 499.2 ppb for boron workers, 96.1 ppb

and 47.9 ppb for workers from high and low environmental boron areas ($p < 0.0001$), respectively. Boron concentrated in seminal fluid. No significant correlations were found between blood or urine boron and adverse semen parameters. No significant statistical differences in total sperm count, sperm concentration, velocity, linearity, motile cells, morphology, head, neck and tail defects in sperm were found. DNA strand breakage measured by the COMET assay and percent apoptotic cells measured by TUNEL assay were similar across the exposure groups. Sperm aneuploidy and diploidy of chromosomes X, Y or 18 did not differ by exposure groups or boron levels in post-workshift urine or blood ($p > 0.05$). Exposure to boron in this area of China did not reach levels causing adverse effects published in animal toxicology work but exceeded those previously published for boron occupational groups. **Summary report.** ([REDACTED], 9/17/17)

50366-0235 302550 “An overview of male reproductive studies of boron with an emphasis on studies of highly exposed Chinese workers.” Anthony R. Scialli, Jens Peter Bonde, Irene Bruske-Hohlfeld, B.Dwight Culver, Yanhong Li and Frank M. Sullivan. Tetra Tech Sciences, 2200 Wilson Boulevard, Suite 400, Arlington, VA 22201-3397, USA, Department of Environmental and Occupational Medicine, Copenhagen University Hospital, Bispebjerg, Copenhagen, Denmark, Munich, Germany, Department of Epidemiology, School of Medicine, University of California, Irvine, CA, USA, Environmental Toxicology Graduate Program, Department of Entomology, University of California, Riverside, CA, USA. *Reproductive Toxicology* 29 (2010) 10-24. The study involved male workers group ($n=70$) from boron mining or boron processing plants in Kuandian City in Liaoning province in northeast China. A subset of 16 of these workers from Pengxiang plant where the drinking water was heavily contaminated with boron was also included. Two control groups were recruited for comparison. The remote background control group ($n=70$) included workers recruited 30 miles away from Kuandian City with low boron exposure levels. The local community control group ($n=63$) included workers without occupational exposure to boron but drawn from the same community as the boron workers. The study included individual assessment of boron exposure, interview data on reproductive experience and semen analysis. Boron content of environmental and biological samples was measured using ICP-AES (Inductively Coupled Plasma-Atomic Emission Spectrometry) and ICP-MS (Inductively Coupled Plasma-Mass Spectrometry). Boron workers had a mean daily intake of 31.3 mg B/day and a subset of 16 of these men employed from Pengxiang plant had an estimated mean daily boron intake of 125 mg B/day. Estimates of mean daily boron intake in local community and remote background controls were 4.25 mg B/day and 1.40 mg B/day, respectively. The average post-shift urine boron concentration was 14.7 mg/B/day in boron workers; 63.3 mg/B/day in 16 boron workers from Pengxiang plant; 4.49 mg/B/day in local community controls and 1.58 mg/B/day in remote background controls. Concentration of boron in serum was 252 ng/B/ml in boron workers, 1558 ng/B/ml in workers with high boron exposure from water contamination, 114 ng/B/ml in local community controls and 39.1 ng/B/ml in remote background controls. The concentration in semen was 592 ng/B/ml in boron workers, 1844 ng/B/ml in highly exposed boron workers, 281 ng/B/ml in local community controls and 146 in remote background controls. There were no significant statistical differences in sperm density, count, motility, velocity, straightness and linearity between boron exposure groups, including the highly exposed group. The Y: X ratio was 0.99 in the remote background control, 0.96 in the local community control and 0.93 in the boron workers which did not correlate with the boron concentration in blood, semen and urine. No clear indication of male reproductive toxicity. **Summary report.** ([REDACTED] 9/19/17)

Summary: Although the studies conducted in rats, mice and humans are not guideline studies, collectively, they provide sufficient information to satisfy information for an acceptable reproduction toxicity study. In conclusion, the studies in rats and mice demonstrate that boron affects the male reproduction and male is the most sensitive sex. However, in humans no significant correlations were found between blood or urine boron and adverse conventional semen parameters. Boron exposure in

highly exposed workers was not as high as the no-effect level in the rat. There is no clear evidence indicating male reproductive toxicity in highly exposed boron workers.

DEVELOPMENTAL TOXICITY

Developmental Toxicity, Rat ** †

50366-082 098311 Price, C.J., Field, E. A., Marr, M. C., Myers, C.B., Morrissey, R. E., and Schwetz, B. A. "Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in Sprague-Dawley rats." Research Triangle Institute, Research Triangle Park, NC., May 1, 1990. Crl:CD® BR VAF/Plus™ Sprague-Dawley rats were dosed with boric acid in diet at 0, 0.1, 0.2, or 0.4% throughout the 20-day gestation period (29 dams/group). Groups of 14 dams were fed 0 or 0.8% boric acid in diets on days 6-15 in a parallel study. Maternal NOEL = 0.1 % (slight increases in kidney weight). The developmental NOEL = was not established (dose-related, statistically significant decreases in mean fetal weight were noted in all groups: also, "shortened rib XIII" and wavy ribs were dose-related at all dose levels). A "possible adverse effect" was indicated by a variety of effects, generally at higher doses, in the absence of marked maternal toxicity. These developmental effects included sharply increased resorptions (0.8% group), late fetal deaths (0.8% group), fetal weights reduced by up to 50% (0.4% and 0.8% groups, respectively), gross malformations: short, curly tail (0.8% group), anophthalmia or microphthalmia (0.8% group); soft tissue malformations: enlarged lateral ventricles (0.4% and 0.8% groups), displaced eyes (0.8% group), various defects of heart and great vessels (0.8% group); skeletal malformations: agenesis of rib XIII (0.4% and 0.8% groups, related to "shortened rib XIII" noted above), fused ribs (0.8% group), cleft sternum (0.2%, 0.4% and 0.8% groups). A number of variations, many of which were ossification delays, were common in the 0.4% and 0.8% groups. Study is not acceptable and not upgradeable (no developmental NOEL). [REDACTED] 1/07/92.

50366-098 131754 Price, C.J., Marr, M.C., and Myers, C.B., "Determination of the No-Observable-Adverse-Effect Level (NOAEL) for developmental toxicity in Sprague-Dawley (CD®) rats exposed to Boric Acid (CAS No. 10043-35-3) in feed on gestational days 0 to 20 and evaluation of postnatal recovery through postnatal day 21," Research Triangle Institute, 8/8/94. RTI ID 65C-5657-200. Boric Acid, 98-99% purity, was administered in diet at 0%, 0.025%, 0.05, 0.075, 0.100 or 0.200% to 60 time-mated Sprague-Dawley female rats/group during gestation days 0 to 20. Scheduled sacrifice for about half of the dams per group was on gestation Day 20 (Phase I), and for the rest on post-natal Day 21 (Phase II, a recovery study). A "possible adverse effect" was seen: this study confirmed findings of the previous study (see Record No. 098311), and identified NOAEL's for maternal and developmental changes. Maternal NOAEL = 0.100% in diet (reduced gravid uterine weight and slightly increased right kidney weight). Developmental NOAEL = 0.075%, based on increased incidence of shortened rib XIII, wavy ribs and reduced fetal body weight. For litters reared to weaning, a postnatal NOAEL = 0.100%, based on increased incidence of shortened rib XIII. This study is not independently acceptable, since is a follow-up study designed with specific objectives. Nevertheless, coupled with Record No. 098311, this report provides a coherent assessment of boric acid developmental toxicity. [REDACTED] and [REDACTED], 12/16/94.

** Overall examination of primary study (50366-082 098311), in conjunction with supplementary study: 50366-098 131754. Title and date of the primary study: "Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in Sprague-Dawley rats," 5/1/90. The primary study, Record No. 098311, was classified as "not acceptable" due to lack of a NOEL. A supplementary study, Record No. 131754, was then undertaken. The latter study identified a NOAEL for maternal and developmental effects, and also assessed postnatal recovery. Collectively, these studies fill the rat teratology study "data gap." Overall, the studies continue to indicate a "possible adverse effect." [REDACTED], 12/16/94.

Developmental Toxicity, Rabbit ** †

** 50366-083 112056 Price, C. J., Marr, M. C., and Myers, C. B., "Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in New Zealand White rabbits." Research Triangle Institute, Nov. 1991. Thirty rabbits/group received 0, 62.5, 125, or 250 mg/kg/day of boric acid (99% purity) by gavage on gestation days 6-19. Maternal NOEL = 125 mg/kg/day (modest reduction in body weight corresponding to modest reduction in food intake). High dose females characteristically had vaginal bleeding over about a 10-day period after cessation of dosing. Three 250 mg/kg/day does aborted (vs. none in other groups): an apparent treatment effect. Developmental NOEL = 62.5 mg/kg/day (agenesis of gall bladder at 125 and 250 mg/kg/day). Main findings at 250 mg/kg/day were resorptions (90% of implants), with cardiovascular malformations in remaining conceptuses (enlarged aorta, interventricular septal defects, pulmonary artery and aorta both arising from right ventricle). Report is acceptable, and identifies possible adverse effects (above malformations) at the highest two dose levels. [REDACTED], 7/24/92, with clarifying edits by [REDACTED] on 2/6/13.

Developmental Toxicity, Mouse ** †

**50366-082 098312 Field, E. A., Price, C. J., Marr, M. C., Myers, C. B., Morrissey, R. E., and Schwetz, B. A. "Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in CD-1-Swiss mice." Research Triangle Institute, Research Triangle Park, NC, Aug. 11, 1989. Crl:CD-1 (ICR) VAF/Plus™ outbred albino Swiss mice were dosed with boric acid in diet at 0, 0.1, 0.2, or 0.4% on days 0-17 p.c. No maternal NOEL was identified, due to dose-related increases in "renal tubule dilatation/regeneration." No developmental NOEL was found, since "pale spleen" was increased, dose-related, in all groups. For both maternal and developmental toxicity, 0.1% in diet appeared to be near to a no-effect level. The study is considered to indicate a "possible adverse effect," since there were increased resorptions at 0.4% [and 100% resorptions in the associated pilot study at 0.8% and above], and also fetal body weight decrements and some skeletal malformations at 0.2% and above (the most conspicuous dose-response being shortened thirteenth rib). The latter findings did not appear to be simply due to maternal toxicity. Acceptable. [REDACTED], 1/07/92, with clarifying edits by [REDACTED] on 2/6/13.

NEUROTOXICITY

Acute Neurotoxicity, Rat

50366-0228 272188 "Single-dose oral (gavage) neurotoxicity limit test of boric acid in Sprague-Dawley rats," IIT Research Institute (IITRI), Chicago, IL, March 7, 2012. IITRI Project No. 2328-001. Ten Crl:CD®(SD) rats/sex/group were dosed once by gavage with boric acid, lot 8C20, 99% purity, at 0 or 2000 mg/kg (limit test) in a standard acute neurotoxicity study. Apparent NOEL = 2000 mg/kg. There were no definitive treatment effects. This report is not acceptable as presented. Concerns about conduct and additional information needed are found in the discussion section of this review. [REDACTED], July 2, 2013.

90-day Neurotoxicity, Rat

There is no study of this category on file.

Developmental Neurotoxicity, Rat

There is no study of this category on file.

Delayed Neurotoxicity, Hen

There is no study of this category on file.

IMMUNOTOXICITY ** †

****50366-0229 272189** Curry, P. T., "Evaluation of the Potential Immunogenic Activity of Boric Acid Using the Sheep Red Blood Cell Plaque Forming Assay in Mice," IIT Research Institute (IITRI), Chicago, IL, March 9, 2012. IITRI Project No. 2328-002. Groups of ten female B₆C₃F₁ mice/group were dosed by gavage for 28 days with 0 or 1000 mg/kg/day boric acid, lot 8C20, 99% purity, in an SRBC plaque forming immunogenicity study. An additional ten mice were administered positive control (cyclophosphamide, 80 mg/kg) 24 hrs before sacrifice. All mice received 2-3 x 10⁸ washed SRBC's iv for the last 4 days before sacrifice. Boric acid treatment did not affect body weight, food consumption, or clinical signs. Isolated splenocytes in RMPI-1640 medium, to which SRBC's and complement were added, were incubated at 37°C for 1 hr prior to plaque counting: plaques indicating lysis of SRBC's from lytic antibodies in sensitized lymphocytes. There was a statistically significant reduction in IgM plaques per 10⁶ live splenocytes (to 52% of negative control for boric acid group). Positive control was effective (reduction to 5% of negative control plaques/live splenocytes). Study is acceptable, with a "possible adverse effect" for immunogenic activity. See follow-up study in Record No. 272190. [REDACTED], July 3, 2013.

****50366-0229 272190** Curry, P. T., "Evaluation of the Potential Immunogenic Activity of Boric Acid Using the Sheep Red Blood Cell Plaque Forming Assay in Mice," IIT Research Institute (IITRI), Chicago, IL, April 4, 2012. IITRI Project No. 2337-001. Groups of ten female B₆C₃F₁ mice/group were dosed by gavage for 28 days with 0, 250, 500, 750, or 1000 mg/kg/day boric acid, lot 8C20, 99% purity, in an SRBC plaque forming immunogenicity study. An additional ten mice were administered positive control (cyclophosphamide, 80 mg/kg) 24 hrs before sacrifice. All mice received 2-3 x 10⁸ washed SRBC's iv for the last 4 days before sacrifice. Isolated splenocytes in RMPI-1640 medium, to which SRBC's and complement were added, were incubated at 37°C for 1 hr prior to plaque counting: plaques indicating lysis of SRBC's from lytic antibodies in sensitized lymphocytes. There were highly statistically significant reductions in IgM plaques per 10⁶ live splenocytes at 750 and 1000 mg/kg/day, and a marginally significant decrease at 500 mg/kg/day (p = 0.031). Although investigators consider this study to be negative, this DPR reviewer considers this study to represent a treatment response with a NOEL of 250 mg/kg/day. Study is acceptable. Indication of an immunotoxic response is a "possible adverse effect." [REDACTED] July 3, 2013.

ENDOCRINE DISRUPTOR STUDIES

There is no study of this category on file.

SUPPLEMENTAL STUDIES

Human Epidemiological Data

50366-088 118238 Whorton, D., Haas, J., and Trent, L., "Reproductive effects of inorganic borates on male employees: Birth rate assessment," ENSR Health Sciences, 3/31/92. A retrospective study showed that wives of workers from a borate mining and processing plant in Boron, CA delivered somewhat more children than expected numbers, based on a national cohort. This result led investigators to conclude that borate exposure to workers had no deleterious effect on their reproductive health. Study provides useful epidemiological information, especially because testicular atrophy and subsequent male infertility had been observed in animal studies. Because of the limited

scope of this study (live births as the sole endpoint), and limitations in design (birth rates compared to national norms, possibly inappropriate for a control population; exposures were only roughly estimated), this study does not substitute for a reproduction study in laboratory animals. [REDACTED], 12/21/94.

50366-088 118456 Whorton, D., Haas, J., and Trent, L., "Reproductive effects of inorganic borates on female employees: Birth rate assessment," ENSR Health Sciences, 3/31/92. This was an offshoot to the study performed to evaluate reproductive effects on male employees (see Record No. 118238), and was presented as Appendix C of that report. The study on female employees also monitored the same endpoints: numbers of live births and sex of offspring compared to the same national database. There were only 68 female participants in this study, thus very limited opportunity to identify treatment effects. Results were not remarkable. The study should be considered as useful epidemiological data, but more limited in statistical power than the corresponding data on male employees. Other limitations noted for the male employee study also apply here. [REDACTED], 12/21/94.

50366-088 118457 Wegman, D.H., Eisen, E. A., and Smith R. G., "Acute and chronic respiratory effects of sodium borate particulate exposures," 1/3/91. Only chronic aspects of this study are summarized here. Pulmonary function studies were conducted in 1981 and 1988 at the U.S. Borax mine near Boron, CA. There were 303 participants with usable tests [forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV₁)] during both time periods. Chief criteria examined were decrements in the above measures over the 7-year period between tests. Estimates were made of dust and borate exposures, based on job classifications. Analyses considered variables such as age and smoking histories. Results indicated no association between exposure and pulmonary function during the 7-year period. Useful information, but not a substitute for animal chronic studies for many reasons, including that exposure was not rigorously characterized, only a single set of endpoints was evaluated (pulmonary function changes), the exposure time frame did not include the whole period of workers' exposure (so that initial pulmonary changes, if any, might be detected). [REDACTED], 12/21/94.

BIOBOR JF

TERATOLOGY, RAT

** **002 088735** Lemen, J. K. "Rat teratology Study with Biobor[®] JF." (Hazleton Laboratories America Incorporated, HLA Study No. 182-129, July 12, 1990.) BIOBOR[®] JF, purity 95%, was administered by gavage at doses of 0 (corn oil), 100, 300, or 1000 mg/kg to 25 mated female Crl:CD[®]BR rats per group 6 through 15 of gestation. Test article was not corrected for purity. **Possible adverse effect:** lower fetal weights and viability; increased incidence of soft tissue variations (dilated ventricles of the brain and renal pelvic cavitation); fetal skeletal variations (incomplete ossified and/or unossified skull, vertebrae, sternbrae, centra, ischium, pubes, metacarpals, metatarsals); vertebral anomalies with and/or without associated rib anomalies - malformations. Developmental NOEL = 100 mg/kg/day (lower fetal weight, visceral variations and skeletal variations and malformations). Maternal NOEL = > 1000 mg/kg/day. ACCEPTABLE. [REDACTED] and [REDACTED], 7/16/03).
US EPA (1993): Developmental NOEL = 100 mg/kg/day; maternal NOEL = 300 mg/kg/day (reduced weight gain at termination of study (possibly due to lower gravid uterine weight)).

TERATOLOGY, RABBIT

50439-002; 088734 Lemen, J. K. "Rabbit teratology Study with Biobor® JF." (Hazleton Laboratories America Incorporated, HLA Study No.182-131, July 11, 1990.) BIOBOR® JF, purity 100% (assumed), was administered by gavage at doses of 0 (corn oil), 25, 75, or 225 mg/kg/day to 17 pregnant New Zealand White Rabbits/group on days 7 through 19 of gestation. No evidence of maternal toxicity was observed. Maternal NOEL = > 225 mg/kg/day. Possible adverse effects (fetuses). At 75 and 225 mg/kg dose levels, fetal skeletal variations related to incomplete ossification and variability in the number of ribs and presacral vertebrae [5th sternebra unossified, absent sternebra(e), and 7th cervical rib(s)] were observed. There was dose-related increase in skeletal variations. Visceral malformations were noted in litters from groups 1, 2 and 4. Visceral malformations included internal hydrocephaly (group 1 fetus), agenesis of diaphragm (group 1 fetus), and agenesis of gall bladder (2 fetuses in group 2 and 4 fetuses in group 4). There was no dose-related increase in visceral or skeletal malformations. Developmental NOEL = 25 mg/kg/day (skeletal variations). Study upgraded to acceptable. (██████████ and ██████████, 7/16/03; upgraded, ██████████ and ██████████, 7/12/17)

GENOTOXICITY

GENE MUTATION

** 004 114605 Lawlor, T.E. "Mutagenicity Test on Biobor® JF in the Ames *Salmonella*/Microsome Reverse Mutation Assay." (Hazleton Laboratories America, Inc., HLA Study No.: 10630-0-401, June 11, 1990) Biobar® JF (95% purity) was tested at concentrations of 0 (corn oil), 0.1, 0.5, 1, 5, 10, 50, and 100 µl/plate for mutagenicity using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 by the plate incorporation assay. There were triplicate plates per concentration with and without rat liver activation. There were two trials. No significant increase of revertants was reported with Biobor® exposure under study conditions. ACCEPTABLE. (██████████ and ██████████, 7/22/03).

The RED of US EPA lists a study with mouse lymphoma that is not on file with the Department. The study is by Microbiological Associates, Lab number NO1-CP-41004, 1988.

CHROMOSOME EFFECTS

004 114604 Ivett, J. L. "Mutagenicity Test on Biobor® JF in the *In Vivo* Mouse Micronucleus Assay." (Hazleton Laboratories America, Incorporated, HLA Study No.: 10630-0-455, March 13, 1989.) Biobor® JF (lot HP 7322, purity not identified) was administered at doses of 0 (corn oil), 500, 2500, or 5000 mg/kg *via* a single gavage to five ICR mice/sex/group. Mice were sacrificed at 24, 48 or 72 hours post-dosing. One thousand polychromatic erythrocytes per animal were scored for micronuclei and the ratio of normochromatic erythrocytes to PCEs determined. The PCE value for high dose males (5000 mg/kg) was statistically significantly higher at 48 hours but considered by the author as a statistical anomaly due to the low micronucleus value in the control compared with the historical control range. Also, there was no time course for an effect. Females did not show any increase in micronuclei. UNACCEPTABLE (dosing material purity needs to be confirmed). Upgradeable. (██████████ and ██████████ 7/22/03).

DNA DAMAGE

004 114606 Cifone, M. A. "Mutagenicity Test on Biobor® JF in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay." (Hazleton Laboratories America, Inc., HLA Study No.: 10630-0-447, February 27, 1989.) Biobor® JF (lot # HP7322, purity not stated) was tested at 101 to 1010 µg/ml

in Assay #2 and 50.6 to 380 µg/ml in a second assay for DNA damage by measuring UDS in primary rat hepatocytes *in vitro*. The first trial was not completed due to poor cell attachment. UDS was evaluated by autoradiography. There were triplicate coverslips per concentration in each trial with 50 cells scored per coverslip for a total of 150 cells per concentration. No significant changes in the nuclear labeling of rat primary hepatocytes. Summary data only were presented. UNACCEPTABLE (the results from individual cultures and the nuclear and cytoplasmic counts and test article purity were not included in the report). Upgradeable. (██████████ and ██████, 7/23/03).

MISCELLANEOUS

SUBCHRONIC, RAT DERMAL

005 114609 Lemen, J. K. "13-Week Dermal Toxicity Study in Rabbits with Biobor[®] JF." (Hazleton Laboratories America, Inc., HLA Study No. 182-133, December 26, 1989.) Biobor[®] JF (lot LH No. 24,064C, purity not given but assumed 100%) was administered at doses of 0, 105, 525, or 1050 mg/kg/day, 5 days/week for 13 weeks. Test material was applied undiluted to the dorsal skin of 10 New Zealand rabbits/sex/group under occluded wrap. The site of treatment application showed one or more signs of dermal irritation at all doses, including some in corn oil controls. Dermal NOEL <105 mg/kg/day. Hematocrit and hemoglobin levels were decreased for high dose females but not for males. There were no treatment-related effects on body weight, food consumption, clinical chemistry, ophthalmology or histopathology other than skin. Systemic NOEL for females = 525 mg/kg/day. UNACCEPTABLE. Upgradeable (confirmation of purity of test article). (██████████ and ██████, 7/24/03).