NATIONAL TOXICOLOGY PROGRAM
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# TOXICOLOGY AND CARCINOGENESIS STUDIES OF BORIC ACID (CAS NO. 10043-35-3) IN B6C3F$_1$ MICE (FEED STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

## NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT

ON THE

# TOXICOLOGY AND CARCINOGENESIS STUDIES OF BORIC ACID

(CAS NO. 10043-35-3)

# IN B6C3F$_1$ MICE

(FEED STUDIES)


NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

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Public Health Service
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## NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis Program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

$B(OH)_3$

# BORIC ACID

CAS No. 10043-35-3

$H_3BO_3$ Molecular weight 61.83

Synonyms: orthoboric acid; boracic acid

## ABSTRACT

Boric acid is a component of cosmetics and pharmaceuticals and is also used in numerous industrial processes. Earlier long-term studies did not demonstrate a carcinogenic effect in Sprague-Dawley rats (Weir and Fisher, 1972). Because of potential widespread human exposure, corroborative evidence was sought in a second species. Toxicology and carcinogenesis studies were conducted by feeding technical-grade boric acid (99.7% pure) to groups of male and female B6C3F$_1$ mice for 14 days, 13 weeks, and 2 years.

In the 14-day studies (five mice per group), mortality occurred in mice fed 25,000 ppm, 50,000 ppm, or 100,000 ppm boric acid; hyperplasia and/or dysplasia of the forestomach was also seen in these dose groups. No compound-related gross pathologic or histopathologic effects were seen in male or female mice exposed at concentrations up to 12,500 ppm in feed. In the 13-week studies, groups of 10 male and 10 female mice were fed boric acid at concentrations up to 20,000 ppm; 8 male mice and 1 female mouse receiving 20,000 ppm and 1 male receiving 10,000 ppm boric acid died before the end of the studies. Male and female mice receiving 20,000 ppm boric acid weighed 23% and 18% less, respectively, than did the controls at the end of the studies. Testicular atrophy in 8/10 male mice, hyperkeratosis and acanthosis of the stomach in 8/10 male and 3/9 female mice, and extramedullary hematopoiesis of the spleen in all male and female mice receiving 20,000 ppm boric acid indicated that the testis, stomach, and spleen were potential target organs in the 2-year studies. Based on these results, 2-year toxicology and carcinogenesis studies were conducted by feeding diets containing boric acid at concentrations of 0, 2,500, or 5,000 ppm to groups of 50 male and 50 female mice.

Survival of high dose male mice after week 63 and of low dose male mice after week 84 was lower than that of controls (final survival: control, 41; low dose, 30; high dose, 22), which may have reduced the sensitivity of the carcinogenicity study; the numbers of female mice (33; 33; 37) that survived to the end of the studies were considered adequate for toxicologic evaluation. Body weight gain was reduced in each sex after week 30; mean final body weights were 7% and 13% below control values for exposed male mice and 7% and 20% below those of controls for exposed female mice. No chemically related clinical signs were reported.

At the top dose, boric acid caused an increased incidence of testicular atrophy (control, 3/49; low dose, 6/50; high dose, 27/47) and interstitial cell hyperplasia (0/49; 0/50; 7/47) in male mice. The testicular atrophy was characterized by variable loss of spermatogonia, primary and secondary spermatocytes, spermatids, and spermatozoa from the seminiferous tubules. The seminiferous tubules contained primarily Sertoli cells and variable numbers of spermatogonia. In some mice, there were accumulations of interstitial cells, indicating hyperplasia.

In low dose male mice, there were increased incidences of hepatocellular carcinomas (5/50; 12/50; 8/49) and hepatocellular adenomas or carcinomas (combined) (14/50; 19/50; 15/49) and an increased incidence of subcutaneous tissue fibromas, sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) (2/50; 10/50; 2/50). No increased incidence of subcutaneous tissue neoplasms was seen in male mice receiving 5,000 ppm. Because the incidence of subcutaneous tissue tumors is variable in historical controls, because there was no corresponding increase in the high dose male mice, and because the incidence of hepatocellular tumors was not significant by the incidental tumor test and was within the historical control range, neither of these tumors was considered to be related to the administration of boric acid.

Boric acid was not mutagenic in the Salmonella/microsome assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537. Boric acid was negative in the mouse lymphoma L5178Y/TK$^{+/-}$ assay and did not induce sister-chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells. All assays were performed with and without metabolic activation.

The data, documents, and pathology materials from the 2-year studies of boric acid were audited at the NTP Archives. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenicity** of boric acid at doses of 2,500 or 5,000 ppm for male or female B6C3F$_1$ mice. Testicular atrophy and interstitial cell hyperplasia were observed in high dose male mice. The decrease in survival of dosed male mice may have reduced the sensitivity of this study.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 8.

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## APPENDIXES

## PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on boric acid on March 26, 1986, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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## SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF BORIC ACID

On March 26, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of boric acid received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. M. Dieter, NTP, introduced the toxicology and carcinogenesis studies of boric acid in mice by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenicity for male or female mice).

Dr. Perera, a principal reviewer, agreed with the conclusions as written. She said that the conclusion should note that survival was significantly decreased in high and low dose males, thus limiting the sensitivity of the study. Dr. Dieter agreed that this would be done [see page 4].

As a second principal reviewer, Dr. Capen agreed with the conclusions.

As a third principal reviewer, Dr. Scala also agreed with the conclusions. He noted that mean feed consumption measurements for group-housed animals may have little value.

In other discussions, Dr. Hooper and Dr. Mirer asked for a fuller discussion of nonneoplastic toxicity, in particular, reproductive toxicity, and said that inclusion of occupational exposure levels ("standards for nuisance dust") would be useful if they can be obtained. Dr. Dieter said that the discussion would be expanded and workplace exposure levels would be sought.

Dr. Perera moved that the Technical Report on boric acid be accepted with the conclusions as written for male and female mice, no evidence of carcinogenicity. Dr. Capen seconded the motion, and it was approved by 10 reviewers with 1 abstention (Dr. Hughes).

## CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Boric Acid is based on the 13- to 16-week studies that began in March 1980 and ended in July 1980 and on the 2-year studies that began in March 1981 and ended in March 1983 at EG&G Mason Research Institute.

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# I. INTRODUCTION

$B(OH)_3$

## BORIC ACID

CAS No. 10043-35-3

$H_3BO_3$ Molecular weight 61.83

Synonyms: orthoboric acid; boracic acid

Boric acid was nominated to the NTP for testing by the Consumer Product Safety Commission and the U.S. Environmental Protection Agency because of its widespread use and human exposure potential. Adequate data were available on the lack of a carcinogenic effect of boric acid in rats based on 2-year studies (Weir and Fisher, 1972). Thus, boric acid was evaluated for carcinogenicity only in mice in the current NTP studies.

Boric acid occurs as the natural mineral sassolite in volcanic waters and hot springs. Boric acid is an inorganic acid that is stable in air and soluble at 0.1 M in water with a pH of 5.1. Boric acid is an important component of cosmetics and pharmaceuticals and is necessary for a variety of industrial processes. It is incorporated into cosmetic products as a preservative, antiseptic, water softener, pH adjuster, emulsifier, neutralizer, stabilizer, buffer, or viscosifier. It is also used as a medicinal astringent and antiseptic for treatment of burns, a weatherproofer for wood, and a fireproofer for fabrics. Boric acid is also used in eyewashes; in the manufacture of cements, crockery, porcelain, enamels, glass, borates, leather, carpets, hats, soaps, artificial gems, and impregnated wicks; in processes such as nickeling baths, printing, dyeing, painting, photography, production of electric condensers, and hardening steel; and as a catalyst for organic reactions (FDA, 1978).

The total U.S. production capacity figures for orthoboric acid were reported to be 236,000 short tons in 1984 (Mannsville Chemical Products Corp., 1984). About 40,000 short tons are expected to be exported, from production of about 139,000 short tons.

The major end use for boric acid is in glass manufacturing, and the second largest outlet is in fire-retardant applications, particularly in cellulosic insulation (Mannsville Chemical Products Corp., 1984). Boric acid is mildly irritating to the eyes and mucous membranes, and a threshold limit value of 10 mg/m$^3$ of total dust has been recommended by the American Conference of Governmental Industrial Hygienists, as for other nuisance particulates. There are no data for occupational exposure levels, but at 10 mg/m$^3$ inhalation exposure, humans would be exposed to a dose of about 1 mg/kg per day.

A tabulation of product formulation data by the Cosmetic, Toiletry, and Fragrance Association (CTFA) listed 142 products containing boric acid; five douches contained greater than 50% dry weight, one hair color rinse and three deodorants contained greater than 5%-10%, and 133 other products contained greater than 0.1%-5% boric acid (CTFA, 1983). The effective concentration of boric acid is presumably reduced below 5% after the products are diluted before use according to manufacturers' instructions. The CTFA recommended a safe upper limit of 5% boric acid additive in cosmetics and that boric acid at this level not be used on infants or injured skin.

Boric acid is registered as an indirect food additive for use in packaging products that contact foods, and tolerances of 8 ppm of total boron from plant fungicides are permissible as residues on citrus fruits (Fed. Regist., 1969). The estimated average daily intake of boron in France, partly from boric acid residues in fruit, was 25 mg per person (Ploquin, 1966).

Boric acid is poorly absorbed through intact skin; absorption is greatly increased through abraded, denuded, or burned skin and through mucous membranes. Ingested boric acid is transported to the blood and accumulates in the

brain, liver, and fat; excretion is by urine, feces, saliva, milk, and perspiration (Pfeiffer and Jenney, 1950). Dermal studies have been conducted in infants with or without diaper rash or with burns (Mulinos et al., 1953; Vignec and Ellis, 1954; Johnstone et al., 1955), and in adult patients with burns (Draize and Kelley, 1959; Schuppli et al., 1971) or vaginitis (Swate and Weed, 1974). Boric acid appeared only in the urine of infants with diaper rash or burns and in adult burn patients, confirming that absorption occurred through the compromised dermal layer. There was no chemical residue in sera of females treated twice daily for 14 days with vaginal inserts of 600 mg boric acid. There are clinical reports of central nervous system toxicity and toxicity to the genito-urinary tract, liver, and skin in humans exposed to boric acid at pharmacologic concentrations. Death has occurred when boric acid was accidentally ingested or used on abraded skin (Goldbloom and Goldbloom, 1953).

The FDA ruled that boric acid was safe but ineffective as an ocular germicide at concentrations up to 5%, safe and effective as a buffer in ophthalmic preparations at the same concentration (FDA, 1980a), but unsafe as a skin protectant, oral antimicrobial, and anorectal antiseptic, based on the absorption of boric acid by damaged skin and mucous membranes, its cumulative toxicity, and slow elimination (FDA, 1980b).

In animal studies, boric acid is classified as relatively nontoxic, the acute $LD_{50}$ value being greater than 4 g/kg when administered orally in Sprague-Dawley and Long-Evans rats (Weir and Fisher, 1972) and greater than 1 g/kg when administered by subcutaneous injection (Mulinos et al., 1953). The $LD_{50}$ value in mice (unspecified strain) was greater than 1 g/kg by either the intravenous or subcutaneous route (Kunkel, 1950).

Administration of boric acid in water by gavage at 1 g/kg per day or in the diet at 10,000 ppm for 21-27 days reduced body weight gain (Roe et al., 1972) and resulted in altered liver, kidney, and brain nucleotide concentrations (Dani et al., 1971). The same high boric acid doses of about 1 g/kg per day caused testicular atrophy and cellular dystrophic changes after either 14 days (Silaev et al., 1977) or 90 days of oral administration (Weir and Fisher, 1972). The no-effect level in the 90-day study was about 100 mg/kg per day, since at 300 mg/kg per day one of five rats showed some testicular atrophy.

Boric acid fed for 14 days to male and female rats at about 700 mg/kg per day resulted in sterility in subsequent mating trials (Weir and Fisher, 1972). Males lacked viable sperm, and there was decreased ovulation in females. Doses of about 67 and 200 mg/kg per day did not affect reproduction through three generations. Krasovskii et al. (1976) showed that ingestion of boric acid in the drinking water at 6 mg/liter (boron equivalents) per day for 6 months also resulted in testicular atrophy and cellular dystrophy in rats.

A variety of cellular enzyme activities in mammalian testes (Lee et al., 1978) and in blood cells, liver, brain, kidney, and muscle were affected by boric acid; the effect was dependent on concentration (CTFA, 1983). Inhibition or stimulation was observed at millimolar or higher concentrations. Hepatic RNA biosynthesis in rats was also stimulated by millimolar concentrations of boric acid in vivo and in vitro (Weser, 1967, 1968).

There were reports of gene reversion in *Escherichia coli* B/r/Sd-4 assays with boric acid (Demerec et al., 1951), but subsequent, more thorough tests by Iyer and Szybalski (1958) in the Sd-4-73 strain failed to confirm the occurrence. Studies by Szybalski (1958) in *E. coli* were also negative for mutagenic activity; Datta et al. (1983) also reported that boric acid was ineffective for stimulation of Tn9 transposition in *E. coli* K12.

In studies conducted by the NTP, boric acid was not mutagenic in either bacteria or cultured mammalian cells. In the *Salmonella typhimurium* assay with strains TA98, TA100, TA1535, or TA1537, negative results were obtained in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 (Appendix C, Table C1; Haworth et al., 1983); boric acid was also negative in the mouse lymphoma L5178Y/$TK^{+/-}$ assay with or without activation by S9 from Aroclor 1254-induced male F344 rat liver (Tables C2 and C3).

There was no induction of sister-chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells with or without activation by S9 from Aroclor 1254-induced male Sprague-Dawley rat liver (Tables C4 and C5).

The carcinogenic potential of boric acid was studied in female BALB/c mice injected intravaginally with about 100 mg/kg twice per week for 50 weeks (Boyland et al., 1966). There were 20 positive controls dosed with 7,12-dimethylbenz(a)anthracene (DMBA), 30 untreated controls, and 20 mice dosed with boric acid. One mouse in the boric acid group, 15 in the DMBA group, and none of the untreated controls had vaginal neoplasms. This preliminary study was not considered adequate to determine the carcinogenicity of boric acid.

A 2-year study of boric acid was conducted in groups of 35 Sprague-Dawley rats of each sex (Weir and Fisher, 1972). Dietary concentrations were 0, 117, 350, or 1,170 ppm in boron equivalents (about 0, 67, 200, and 669 mg/kg per day). There were no toxicologic effects or histopathologic changes in the two lowest dose groups. Animals receiving the high dose of boric acid had decreased feed consumption, retarded growth, rough hair coats, postural abnormalities, swollen paws, and inflamed, bleeding eyes, as well as hematologic disturbances. The male rats had shrunken scrota and atrophic testes. There was no histopathologic evidence of carcinogenicity.

*Study Rationale:* The 2-year studies of boric acid in Sprague-Dawley rats by Weir and Fisher (1972) were considered adequate carcinogenesis studies, although no historical data base was available for comparison and the chemical was tested in only one species. To complete the test for potential carcinogenicity, the NTP conducted short-term tests and 2-year toxicology and carcinogenesis studies of boric acid in B6C3F$_1$ mice.

# II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF BORIC ACID

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

FIRST FOURTEEN-DAY STUDIES

SECOND FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

## PROCUREMENT AND CHARACTERIZATION OF BORIC ACID

Technical-grade boric acid was obtained in one batch from Thompson Haywood Chemicals (Kansas City, Missouri). Purity and identity determinations were conducted at Midwest Research Institute (Kansas City, Missouri) (Appendix D).

This batch of study material was obtained as a colorless, crystalline solid with a melting point of approximately 165° C. The identity of boric acid was confirmed by elemental analysis and infrared and ultraviolet/visible spectroscopy (Appendix D). The data were consistent with a literature spectrum and the structure of boric acid.

Cumulative data indicated that this batch of boric acid was approximately 99.7% pure. The elemental analysis for boron gave a value in agreement with theory. Spark source mass spectrometry indicated that the two significant metal impurities were silicon (~0.18%) and potassium (~0.16%). Weight loss on drying over silica gel indicated that the study material contained 0.03% water. Titration with sodium hydroxide indicated a purity of 99.7%.

The study material was determined to be stable for 2 weeks at 60° C. Therefore, it was recommended that the study material be stored at ambient temperatures for the duration of the toxicity studies. The boric acid study material was stored at 0° ± 5° C at the study laboratory. Periodic characterization of the boric acid study material and a reference standard stored at −20° C by infrared spectroscopy and titration indicated no degradation over the course of the toxicity studies.

## PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

Boric acid was accurately weighed, added to an aliquot of NIH 07 Rat and Mouse Ration in a mortar, and mixed with a pestle. This premix was sandwiched between the remaining meal in a pin intensifier bar model Patterson-Kelly® V-blender and mixed for 15 minutes (5 minutes with the intensifier bar on, 10 minutes with the intensifier bar off). Formulated diets were analyzed for boric acid content by the azomethine H method for the determination of boron (John et al., 1975). This method involves the extraction of formulated diets with 50% aqueous methanol followed by treatment of the extract with an azomethine color-developing solution. The absorbance of the resultant solution was read at 420 nm. Formulated diets were found to be homogenous. Further studies demonstrated that boric acid feed blends were stable for 2 weeks when stored, sealed, and protected from light at 5° C (Appendix E). The formulated diets were stored at 0° ± 5° C for no longer than 2 weeks.

Periodic analyses of formulated diets by the method described above were performed at the study and analytical chemistry laboratories (Appendixes F and G) to determine if the feed mixtures contained the correct concentrations of boric acid. Formulated diets were analyzed once during the 13-week studies. The results ranged from 91% to 101% of target concentrations (Table G1). All dose mixtures analyzed during the 2-year studies were within 10% of the target concentration (Table 1; Table G2). It is therefore concluded that dose mixtures were prepared within specifications throughout the studies. Referee analyses were periodically performed by the analytical chemistry laboratory. Results from the two laboratories were generally in close agreement (Table G3).

## FIRST FOURTEEN-DAY STUDIES

Male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 15 days before the studies began. The mice were 6-8 weeks old when placed on study. Groups of five males and five females were fed diets containing 0, 600, 1,200, 2,400, 4,900, or 9,800 ppm boric acid for 14 consecutive days.

TABLE 1. SUMMARY OF RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF BORIC ACID

| | Target Concentration (ppm) | |
|---|---|---|
| | 2,500 | 5,000 |
| Mean (ppm) | 2,521 | 5,034 |
| Standard deviation | 106 | 137 |
| Coefficient of variation (percent) | 4.2 | 2.7 |
| Range (ppm) | 2,370-2,730 | 4,780-5,210 |
| Number of samples | 14 | 14 |

Animals were weighed on days 1, 7, and 15. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 2.

## SECOND FOURTEEN-DAY STUDIES

Male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories and held for 20 days before the studies began. The mice were 7-9 weeks old when placed on study. Groups of five males and five females were fed diets containing 0, 6,200, 12,500, 25,000, 50,000, or 100,000 ppm boric acid for 14 consecutive days. Animals were weighed on days 1, 7, and 15. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 2.

## THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to boric acid and to determine the concentrations to be used in the 2-year studies.

Four- to five-week-old male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 3 weeks, and assigned to cages such that average cage weights for each sex were approximately equal. Diets containing 0, 1,200, 2,500, 5,000, 10,000, or 20,000 ppm boric acid were fed to groups of 10 mice of each sex for 13 weeks. The 1,200-, 2,500-, 5,000-, and 10,000-ppm groups were fed formulated diets for up to 3 additional weeks. Mice were housed five per cage. Formulated or control diets and water were available ad libitum. Further experimental details are summarized in Table 2.

Animals were checked two times per day; moribund animals were killed. Feed consumption was measured weekly by cage. Individual animal weights were recorded weekly.

After 13-14 weeks, survivors in the control and 20,000-ppm groups were killed. Animals in the other dosed groups continued to receive formulated diets until they were killed (between week 14 and week 17). A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 2.

## TWO-YEAR STUDIES

### Study Design

Diets containing 0, 2,500, or 5,000 ppm boric acid were fed to groups of 50 male and 50 female mice of each sex for 103 weeks.

### Source and Specifications of Animals

The male and female $B6C3F_1$ (C57BL/6N, female × C3H/HeN $MTV^-$, male) mice used in these studies were produced under strict barrier conditions at Frederick Cancer Research Center under a contract to the Carcinogenesis Program. Breeding stock for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms The mice were shipped to the study laboratory at 5 weeks of age. The mice were quarantined at the study laboratory for 2 weeks. Thereafter, a complete

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF BORIC ACID

| First Fourteen-Day Studies | Second Fourteen-Day Studies | Thirteen-Week Studies | Two-Year Studies |
|---|---|---|---|
| **EXPERIMENTAL DESIGN** | | | |
| **Size of Study Groups** | | | |
| 5 males and 5 females | 5 males and 5 females | 10 males and 10 females | 50 males and 50 females |
| **Doses** | | | |
| 0, 600, 1,200, 2,400, 4,900, or 9,800 ppm boric acid in feed | 0, 6,200, 12,500, 25,000, 50,000, or 100,000 ppm boric acid in feed | 0, 1,200, 2,500, 5,000, 10,000, or 20,000 ppm boric acid in feed | 0, 2,500, or 5,000 ppm boric acid in feed |
| **Date of First Dose** | | | |
| 8/14/79 | 12/12/79 | 3/14/80 | 3/26/81 |
| **Date of Last Dose** | | | |
| 8/27/79 | 12/25/79 | 6/13/80-6/28/80 | 3/18/83 |
| **Duration of Dosing** | | | |
| 14 consecutive d | Same as first 14-d studies | 5 d/wk for 13 wk for 0- and 20,000-ppm groups; other groups up to 16 wk | 103 wk |
| **Type and Frequency of Observation** | | | |
| Observed 2 × d; weighed on d 1, 7, and 15 | Same as first 14-d studies | Observed 2 × d; weighed initially, 1 × wk thereafter | Observed 2 × d; weighed 1 × wk for 12 wk; then 1 × 4 wk |
| **Necropsy and Histologic Examination** | | | |
| Necropsy and histologic examination performed on all animals | Necropsy performed on all animals; histologic exam performed on selected tissues from animals in 25,000-, 50,000-, and 100,000-ppm groups; tissues examined included forestomach and brain | Necropsy and histologic examination performed on all animals; the following tissues examined: gross lesions and tissue masses, mandibular lymph nodes, mammary gland, skin, salivary glands, sternebrae, thyroid gland, parathyroids, small intestine, colon, liver, prostate/testes or ovaries/uterus, lungs and bronchi, heart, pancreas, esophagus, stomach, brain, thymus, trachea, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, spinal cord (if neurologic signs present), eyes (if grossly abnormal), and gallbladder | Necropsy performed on all animals; the following tissues examined histologically for all control and high dose animals and for low dose animals dying before end of studies: tissue masses, abnormal regional lymph nodes, skin, mandibular and mesenteric lymph nodes, mammary gland, salivary glands, vertebrae, bone marrow, costochondral junction, thymus, larynx, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, ileum, colon, liver, gallbladder, pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, pituitary gland. The following tissues examined histologically for low dose mice: lung, liver, stomach, kidney, salivary glands, testis, pancreas, and brain for males and lung, liver, ovary, and brain for females |
| **ANIMALS AND ANIMAL MAINTENANCE** | | | |
| **Strain and Species** | | | |
| $B6C3F_1$ mice | $B6C3F_1$ mice | $B6C3F_1$ mice | $B6C3F_1$ mice |
| **Animal Source** | | | |
| Charles River Breeding Laboratories (Portage, MI) | Charles River Breeding Laboratories (Portage, MI) | Charles River Breeding Laboratories (Portage, MI) | Frederick Cancer Research Center (Frederick, MD) |

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF BORIC ACID (Continued)

| First Fourteen-Day Studies | Second Fourteen-Day Studies | Thirteen-Week Studies | Two-Year Studies |
|---|---|---|---|
| **ANIMALS AND ANIMAL MAINTENANCE (Continued)** | | | |
| **Study Laboratory** | | | |
| EG&G Mason Research Institute (Worcester, MA) | EG&G Mason Research Institute (Worcester, MA) | EG&G Mason Research Institute (Worcester, MA) | EG&G Mason Research Institute (Worcester, MA) |
| **Method of Animal Identification** | | | |
| Ear punch | Ear punch | Ear punch | Ear punch |
| **Time Held Before Study** | | | |
| 15 d | 20 d | 3 wk | 2 wk |
| **Age When Placed on Study** | | | |
| 6-8 wk | 7-9 wk | 7-8 wk | 7 wk |
| **Age When Killed** | | | |
| 8-10 wk | 9-11 wk | 21-26 wk | 111-112 wk |
| **Necropsy Dates** | | | |
| Not performed | 12/27/79 | 6/20/80-7/5/80 | 3/25/83-4/6/83 |
| **Method of Animal Distribution** | | | |
| Animals assigned to cages such that cage weights for each sex were approximately equal | Same as first 14-d studies | Same as first 14-d studies | Assigned to cages according to a table of random numbers |
| **Feed** | | | |
| Wayne Lab Blox® (Allied Mills, Chicago, IL) | Same as first 14-d studies | NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum | Same as 13-wk studies |
| **Bedding** | | | |
| Aspen Bed® (American Excelsior, Baltimore, MD) | Same as first 14-d studies | Same as first 14-d studies when available; otherwise Beta Chips® (Agway, Inc., Syracuse, NY) | Same as first 14-d studies |
| **Water** | | | |
| Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum | Same as first 14-d studies | Same as first 14-d studies | Same as first 14-d studies |
| **Cages** | | | |
| Polycarbonate (Lab Products, Inc., Garfield, NJ) | Same as first 14-d studies | Polycarbonate (See-Through II System, Lab Products, Rochelle Park, NJ) | Same as 13-wk studies |
| **Cage Filters** | | | |
| Nonwoven fiber filters (Lab Products, Inc.) | Same as first 14-d studies | Nonwoven fiber filters (Snow Filtration, Cincinnati, OH) | Same as 13-wk studies |
| **Animals per Cage** | | | |
| 5 | 5 | 5 | 5 |
| **Other Chemicals on Study in the Same Room** | | | |
| None | None | None | None |
| **Animal Room Environment** | | | |
| Temp--20.0°-28.9° C; hum--35%-65%; fluorescent light 12 h/d; 10 room air changes/h | Temp--20.0°-28.9° C; hum--11%-38%; fluorescent light 12 h/d; 10-12 room air changes/h | Temp--21°-28° C; hum--42%-78%; fluorescent light 12 h/d; 12 room air changes/h | Temp--mean, 23.3° C; range, 21°-28° C; hum--mean, 45.4%; range, 5%-79%; fluorescent light 12 h/d |

necropsy was performed on five animals of each sex to assess their health status. The mice were placed on study at 7 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix H).

### Animal Maintenance

Mice were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 2.

### Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 2.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

### Statistical Methods

*Data Recording:* Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

*Survival Analyses:* The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used

the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

*Calculation of Incidence:* The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

*Analysis of Tumor Incidence:* Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided.

Life Table Analysis--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analysis--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals on which a necropsy was actually performed during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

*Historical Control Data:* Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical

control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

# III. RESULTS

FIRST FOURTEEN-DAY STUDIES

SECOND FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Body Weights and Clinical Signs
- Survival
- Pathology and Statistical Analyses of Results

## FIRST FOURTEEN-DAY STUDIES

All the mice lived to the end of the studies (Table 3). Five of five male mice and 1/5 female mice that received 9,800 ppm either lost weight or gained no weight. Final mean body weights of mice that received 4,900 ppm were not adversely affected. No compound-related gross or microscopic pathologic effects were observed. These studies were considered inadequate, and additional 14-day studies were conducted at higher doses to better characterize the 14-day toxicity of boric acid.

## SECOND FOURTEEN-DAY STUDIES

Five of five males and 4/5 females that received 100,000 ppm, 3/5 males that received 50,000 ppm, and 1/5 males that received 25,000 ppm boric acid died before the end of the studies (Table 4). Animals were lethargic with discolored spleen, liver, and renal medullae. Final mean body weights of males that received 25,000 or 50,000 ppm and of females that received 100,000 ppm were more than 10% lower than those of the controls. There was no compound-related effect on feed consumption. Hyperplasia and/or dysplasia of the forestomach was seen in 3/5 males and 2/5 females that received 25,000 ppm, 2/4 males and 2/3 females that received 50,000 ppm, and 4/4 males and 2/2 females that received 100,000 ppm.

Because of mortality and body weight loss in mice fed 25,000-100,000 ppm boric acid in the 14-day studies, the high dose selected for 13-week studies was 20,000 ppm.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FIRST FOURTEEN-DAY FEED STUDIES OF BORIC ACID

| Concentration (ppm) | Survival (a) | Mean Body Weights (grams) Initial (b) | Final | Change (c) | Final Weight Relative to Controls (percent) |
|---|---|---|---|---|---|
| **MALE** | | | | | |
| 0 | 5/5 | 25.2 ± 1.2 | 27.4 ± 1.1 | +2.2 ± 0.7 | -- |
| 600 | 5/5 | 26.8 ± 0.9 | 28.4 ± 1.2 | +1.6 ± 0.5 | 103.6 |
| 1,200 | 5/5 | 26.9 ± 0.7 | 26.8 ± 1.2 | −0.1 ± 1.4 | 97.8 |
| 2,400 | 5/5 | 26.8 ± 0.9 | 28.6 ± 0.9 | +1.8 ± 0.5 | 104.4 |
| 4,900 | 5/5 | 26.7 ± 0.8 | 27.8 ± 0.9 | +1.1 ± 0.2 | 101.5 |
| 9,800 | 5/5 | 26.5 ± 0.6 | 25.2 ± 0.2 | −1.3 ± 0.5 | 92.0 |
| **FEMALE** | | | | | |
| 0 | 5/5 | 20.2 ± 0.4 | 20.4 ± 0.5 | +0.2 ± 0.2 | -- |
| 600 | 5/5 | 20.3 ± 0.5 | 21.4 ± 0.7 | +1.1 ± 0.5 | 104.9 |
| 1,200 | 5/5 | 20.7 ± 0.5 | 21.8 ± 0.5 | +1.1 ± 0.3 | 106.9 |
| 2,400 | 5/5 | 20.0 ± 0.2 | 21.0 ± 0.3 | +1.0 ± 0.2 | 102.9 |
| 4,900 | 5/5 | 20.4 ± 0.3 | 22.2 ± 0.5 | +1.8 ± 0.3 | 108.8 |
| 9,800 | 5/5 | 20.1 ± 0.2 | 20.8 ± 0.4 | +0.7 ± 0.3 | 102.0 |

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SECOND FOURTEEN-DAY FEED STUDIES OF BORIC ACID

| Conc. (ppm) | Survival (a) | Mean Body Weights (grams) Initial (b) | Final | Change (c) | Final Weight Relative to Controls (percent) | Feed Consumption (d) Week 1 | Week 2 |
|---|---|---|---|---|---|---|---|
| **MALE** | | | | | | | |
| 0 | 5/5 | 27.4 ± 1.1 | 29.9 ± 0.9 | +2.5 ± 0.5 | -- | 6.0 | 5.7 |
| 6,200 | 5/5 | 27.6 ± 1.1 | 28.4 ± 1.1 | +0.8 ± 0.3 | 95.0 | 7.4 | 7.2 |
| 12,500 | 5/5 | 27.8 ± 1.0 | 28.8 ± 0.9 | +1.0 ± 0.5 | 96.3 | 10.5 | 12.2 |
| 25,000 | (e) 4/5 | 27.6 ± 0.8 | 26.3 ± 1.4 | −1.8 ± 1.2 | 88.0 | 11.9 | 13.4 |
| 50,000 | (f) 2/5 | 27.4 ± 0.7 | 24.6 ± 0.2 | −2.9 ± 0.8 | 82.3 | 10.6 | 10.5 |
| 100,000 | (g) 0/5 | 27.3 ± 0.4 | (h) | (h) | (h) | 25.0 | (h) |
| **FEMALE** | | | | | | | |
| 0 | 5/5 | 20.3 ± 0.5 | 22.3 ± 0.8 | +2.0 ± 0.3 | -- | 10.5 | 6.5 |
| 6,200 | 5/5 | 20.1 ± 0.4 | 22.0 ± 0.9 | +1.9 ± 0.6 | 98.7 | 8.6 | 7.7 |
| 12,500 | 5/5 | 20.1 ± 0.5 | 21.3 ± 0.3 | +1.2 ± 0.3 | 95.5 | 11.7 | 12.6 |
| 25,000 | 5/5 | 20.2 ± 0.6 | 20.7 ± 0.9 | +0.5 ± 0.5 | 92.8 | 14.6 | 14.5 |
| 50,000 | 5/5 | 20.4 ± 0.5 | 21.3 ± 0.8 | +0.9 ± 0.3 | 95.5 | 15.6 | 15.1 |
| 100,000 | (i) 1/5 | 20.2 ± 0.3 | 18.4 | −1.3 | 82.5 | 12.7 | 3.9 |

(a) Number surviving/number initially in group
(b) Initial group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Grams per animal per day
(e) Day of death: 13
(f) Day of death: 8,14,14
(g) Day of death: 7,7,8,13,14
(h) No data are reported due to the 100% mortality in this group.
(i) Day of death: 9,11,11,11

## THIRTEEN-WEEK STUDIES

Eight of 10 males and 6/10 females that received 20,000 ppm boric acid and 1/10 males that received 10,000 ppm died before the end of the studies (Table 5). Animals displayed nervousness and, at the high doses, were thin, haunchy, and dehydrated with foot lesions and scaly tails. The final mean body weights of mice that received 5,000, 10,000, or 20,000 ppm were 10%, 17%, or 23% lower than that of the controls for males and 8%, 10%, or 18% lower for females. Because large amounts of feed were scratched out of feeders by animals that received 10,000 or 20,000 ppm, the feed consumption values are unreliable.

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF BORIC ACID

| Conc. (ppm) | Survival (a) | Mean Body Weights (grams) Initial (b) | Final | Change (c) | Final Weight Relative to Controls (percent) | Feed Consumption (d) Week 4 | Week 12 |
|---|---|---|---|---|---|---|---|
| **MALE** | | | | | | | |
| 0 | 10/10 | 26.3 | 38.0 | +11.7 | -- | 161 | 140 |
| 1,200 | 10/10 | 26.6 | 36.8 | +10.2 | 96.8 | 156 | 165 |
| 2,500 | 10/10 | 26.7 | 37.2 | +10.5 | 97.9 | 164 | 164 |
| 5,000 | 10/10 | 26.7 | 34.0 | +7.3 | 89.5 | 171 | 199 |
| 10,000 | (e) 9/10 | 26.3 | 31.5 | +5.2 | 82.9 | 193 | 456 |
| 20,000 | (f) 2/10 | 26.4 | 29.1 | +2.7 | 76.6 | 423 | 753 |
| **FEMALE** | | | | | | | |
| 0 | 10/10 | 20.4 | 29.8 | +9.4 | -- | 222 | 190 |
| 1,200 | 10/10 | 20.1 | 28.5 | +8.4 | 95.6 | 264 | 229 |
| 2,500 | 10/10 | 20.2 | 28.5 | +8.3 | 95.6 | 240 | 219 |
| 5,000 | 10/10 | 20.3 | 27.5 | +7.2 | 92.3 | 297 | 271 |
| 10,000 | 10/10 | 20.1 | 26.7 | +6.6 | 89.6 | 321 | 431 |
| 20,000 | (g) 4/10 | 20.2 | 24.3 | +4.1 | 81.5 | 560 | 1,138 |

(a) Number surviving/number initially in group
(b) Initial group body weight
(c) Mean body weight change of the group
(d) Grams of feed consumed per kilogram of body weight per animal per day
(e) Week of death: 2
(f) Week of death: 1,2,2,2,3,3,6,8
(g) Week of death: 1,2,3,3,5,6

Extramedullary hematopoiesis of the spleen of minimal to mild severity in dosed males and dosed females, hyperkeratosis and/or acanthosis of the stomach in high dose males and high dose females, and testicular degeneration or atrophy of the seminiferous tubules in the three highest dose groups of males were observed at increased incidences compared with those in the controls (Table 6).

*Dose Selection Rationale:* Because of weight gain depression in dosed groups, the high incidence of testicular atrophy in males above 5,000 ppm, and extramedullary hematopoiesis of the spleen in all dosed groups, concentrations selected for mice for the 2-year studies were 2,500 and 5,000 ppm boric acid in feed.

TABLE 6. NUMBER OF MICE WITH NONNEOPLASTIC LESIONS IN THE THIRTEEN-WEEK FEED STUDIES OF BORIC ACID

| Site/Lesion | Control | 1,200 ppm | 2,500 ppm | 5,000 ppm | 10,000 ppm | 20,000 ppm |
|---|---|---|---|---|---|---|
| **MALE** | | | | | | |
| Number examined | 10 | 10 | 10 | 10 | 10 | 10 |
| Spleen | | | | | | |
| Extramedullary hematopoiesis | 1 | 3 | 5 | 5 | 10 | 1 |
| Testis | | | | | | |
| Degeneration or atrophy of seminiferous tubules | 0 | 0 | 0 | 2 | 8 | 8 |
| Stomach | | | | | | |
| Hyperkeratosis and/or acanthosis | 0 | 0 | 0 | 0 | 0 | 8 |
| **FEMALE** | | | | | | |
| Number examined | 10 | 10 | 10 | 10 | 10 | 9 |
| Spleen | | | | | | |
| Extramedullary hematopoiesis | 0 | 2 | 4 | 6 | 10 | 2 |
| Stomach | | | | | | |
| Hyperkeratosis and/or acanthosis | 0 | 0 | 0 | 0 | 0 | 3 |

## TWO-YEAR STUDIES

### Body Weights and Clinical Signs

Mean body weights of high dose male mice were 10%-17% lower than those of the controls after week 32 (Table 7 and Figure 1). The mean body weights of high dose female mice were 10%-17% lower than those of the controls after week 52. The average daily feed consumption by low dose and high dose male mice was 118% and 160% that of the controls and by low dose and high dose female mice, 118% and 136% that of the controls (Appendix I, Tables I1 and I2). The average amount of boric acid consumed per day was approximately 400-500 mg/kg or 1,100-1,200 mg/kg for low dose or high dose mice. No compound-related clinical signs were observed.

TABLE 7. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF BORIC ACID

| Weeks on Study | Control | | 2,500 ppm | | | 5,000 ppm | | |
|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (grams) | No. of Survivors | Av. Wt. (grams) | Wt. (percent of controls) | No. of Survivors | Av. Wt. (grams) | Wt. (percent of controls) | No. of Survivors |
| **MALE** | | | | | | | | |
| 0 | 21.7 | 50 | 21.6 | 100 | 50 | 21.8 | 100 | 50 |
| 1 | 23.8 | 50 | 24.1 | 101 | 50 | 23.6 | 99 | 50 |
| 2 | 24.9 | 50 | 25.7 | 103 | 50 | 25.3 | 102 | 50 |
| 3 | 24.6 | 50 | 25.2 | 102 | 50 | 24.1 | 98 | 50 |
| 4 | 26.7 | 50 | 27.7 | 104 | 50 | 27.6 | 103 | 50 |
| 5 | 27.5 | 50 | 28.5 | 104 | 50 | 28.6 | 104 | 50 |
| 6 | 28.5 | 50 | 29.5 | 104 | 50 | 28.4 | 100 | 50 |
| 7 | 29.1 | 50 | 29.7 | 102 | 50 | 29.7 | 102 | 50 |
| 8 | 29.7 | 50 | 30.5 | 103 | 49 | 30.1 | 101 | 50 |
| 9 | 30.1 | 50 | 31.3 | 104 | 49 | 30.5 | 101 | 50 |
| 10 | 30.5 | 50 | 31.6 | 104 | 49 | 30.6 | 100 | 50 |
| 11 | 30.9 | 50 | 31.4 | 102 | 49 | 30.2 | 98 | 50 |
| 12 | 31.1 | 50 | 31.3 | 101 | 49 | 30.1 | 97 | 50 |
| 16 | 33.1 | 50 | 32.9 | 99 | 49 | 32.5 | 98 | 44 |
| 20 | 33.9 | 50 | 33.0 | 97 | 49 | 30.3 | 89 | 44 |
| 24 | 35.6 | 50 | 34.2 | 96 | 49 | 30.6 | 86 | 44 |
| 28 | 37.9 | 50 | 38.1 | 101 | 49 | 34.8 | 92 | 43 |
| 32 | 38.8 | 50 | 39.0 | 101 | 49 | 35.0 | 90 | 43 |
| 36 | 39.8 | 50 | 39.8 | 100 | 49 | 35.3 | 89 | 42 |
| 40 | 41.1 | 50 | 40.8 | 99 | 49 | 35.4 | 86 | 42 |
| 44 | 41.1 | 50 | 40.8 | 99 | 49 | 35.7 | 87 | 40 |
| 48 | 41.0 | 49 | 42.1 | 103 | 49 | 36.9 | 90 | 40 |
| 52 | 43.4 | 49 | 42.5 | 98 | 49 | 38.3 | 88 | 38 |
| 56 | 43.9 | 48 | 41.9 | 95 | 49 | 37.6 | 86 | 37 |
| 60 | 44.1 | 48 | 42.5 | 96 | 49 | 37.6 | 85 | 37 |
| 64 | 43.3 | 48 | 41.5 | 96 | 48 | 37.4 | 86 | 34 |
| 68 | 43.7 | 48 | 41.2 | 94 | 47 | 36.7 | 84 | 34 |
| 72 | 43.4 | 48 | 40.9 | 94 | 46 | 36.3 | 84 | 33 |
| 76 | 42.8 | 48 | 39.9 | 93 | 45 | 37.1 | 87 | 33 |
| 80 | 43.1 | 48 | 39.3 | 91 | 44 | 37.4 | 87 | 31 |
| 84 | 43.0 | 48 | 40.7 | 95 | 41 | 38.0 | 88 | 30 |
| 89 | 42.0 | 48 | 40.7 | 97 | 38 | 37.3 | 89 | 29 |
| 92 | 42.6 | 47 | 39.9 | 94 | 38 | 37.3 | 88 | 27 |
| 96 | 42.3 | 45 | 37.4 | 88 | 37 | 35.2 | 83 | 25 |
| 100 | 41.7 | 43 | 39.5 | 95 | 35 | 36.5 | 88 | 24 |
| 104 | 42.0 | 41 | 39.1 | 93 | 30 | 36.5 | 87 | 22 |
| **FEMALE** | | | | | | | | |
| 0 | 17.6 | 50 | 17.7 | 101 | 50 | 17.1 | 97 | 50 |
| 1 | 18.7 | 50 | 18.5 | 99 | 50 | 18.4 | 98 | 50 |
| 2 | 20.4 | 50 | 19.9 | 98 | 50 | 19.7 | 97 | 50 |
| 3 | 20.2 | 50 | 20.4 | 101 | 50 | 20.5 | 101 | 49 |
| 4 | 21.6 | 50 | 21.7 | 100 | 50 | 21.3 | 99 | 49 |
| 5 | 22.3 | 50 | 22.1 | 99 | 50 | 22.1 | 99 | 49 |
| 6 | 22.9 | 50 | 22.8 | 100 | 50 | 22.0 | 96 | 49 |
| 7 | 23.4 | 50 | 23.1 | 99 | 50 | 23.3 | 100 | 49 |
| 8 | 23.7 | 50 | 24.0 | 101 | 50 | 23.7 | 100 | 49 |
| 9 | 23.9 | 50 | 24.0 | 100 | 50 | 24.1 | 101 | 49 |
| 10 | 24.4 | 50 | 24.3 | 100 | 50 | 24.0 | 98 | 49 |
| 11 | 24.5 | 50 | 24.3 | 99 | 50 | 24.1 | 98 | 49 |
| 12 | 25.0 | 50 | 24.7 | 99 | 50 | 24.7 | 99 | 49 |
| 16 | 27.0 | 50 | 26.4 | 98 | 48 | 25.9 | 96 | 49 |
| 20 | 28.0 | 50 | 27.0 | 96 | 48 | 25.8 | 92 | 49 |
| 24 | 29.7 | 50 | 28.3 | 95 | 48 | 26.1 | 88 | 49 |
| 28 | 31.7 | 50 | 30.3 | 96 | 48 | 28.5 | 90 | 49 |
| 32 | 33.2 | 50 | 30.8 | 93 | 48 | 29.6 | 89 | 49 |
| 36 | 33.1 | 50 | 31.8 | 96 | 48 | 29.9 | 90 | 49 |
| 40 | 35.6 | 50 | 33.3 | 94 | 48 | 30.3 | 85 | 49 |
| 44 | 36.1 | 50 | 33.3 | 92 | 48 | 31.2 | 86 | 49 |
| 48 | 35.2 | 50 | 34.1 | 97 | 48 | 32.3 | 92 | 49 |
| 52 | 38.9 | 50 | 36.3 | 93 | 48 | 33.7 | 87 | 49 |
| 56 | 39.4 | 49 | 36.8 | 93 | 48 | 33.9 | 86 | 49 |
| 60 | 40.9 | 49 | 37.8 | 92 | 48 | 34.6 | 85 | 49 |
| 64 | 39.6 | 49 | 37.7 | 95 | 48 | 34.8 | 88 | 49 |
| 68 | 40.2 | 49 | 37.5 | 93 | 47 | 34.4 | 86 | 49 |
| 72 | 40.6 | 48 | 38.4 | 95 | 46 | 33.8 | 83 | 48 |
| 76 | 40.7 | 48 | 38.4 | 94 | 44 | 34.4 | 85 | 48 |
| 80 | 39.7 | 47 | 38.0 | 96 | 43 | 33.5 | 84 | 48 |
| 84 | 41.7 | 46 | 40.2 | 96 | 42 | 36.2 | 87 | 48 |
| 89 | 42.8 | 46 | 39.7 | 93 | 42 | 35.2 | 82 | 47 |
| 92 | 41.6 | 45 | 40.1 | 96 | 41 | 35.4 | 85 | 45 |
| 96 | 41.9 | 42 | 40.1 | 96 | 39 | 35.3 | 84 | 43 |
| 100 | 43.7 | 38 | 40.4 | 92 | 35 | 37.1 | 85 | 40 |
| 104 | 44.8 | 33 | 41.8 | 93 | 33 | 35.9 | 80 | 37 |

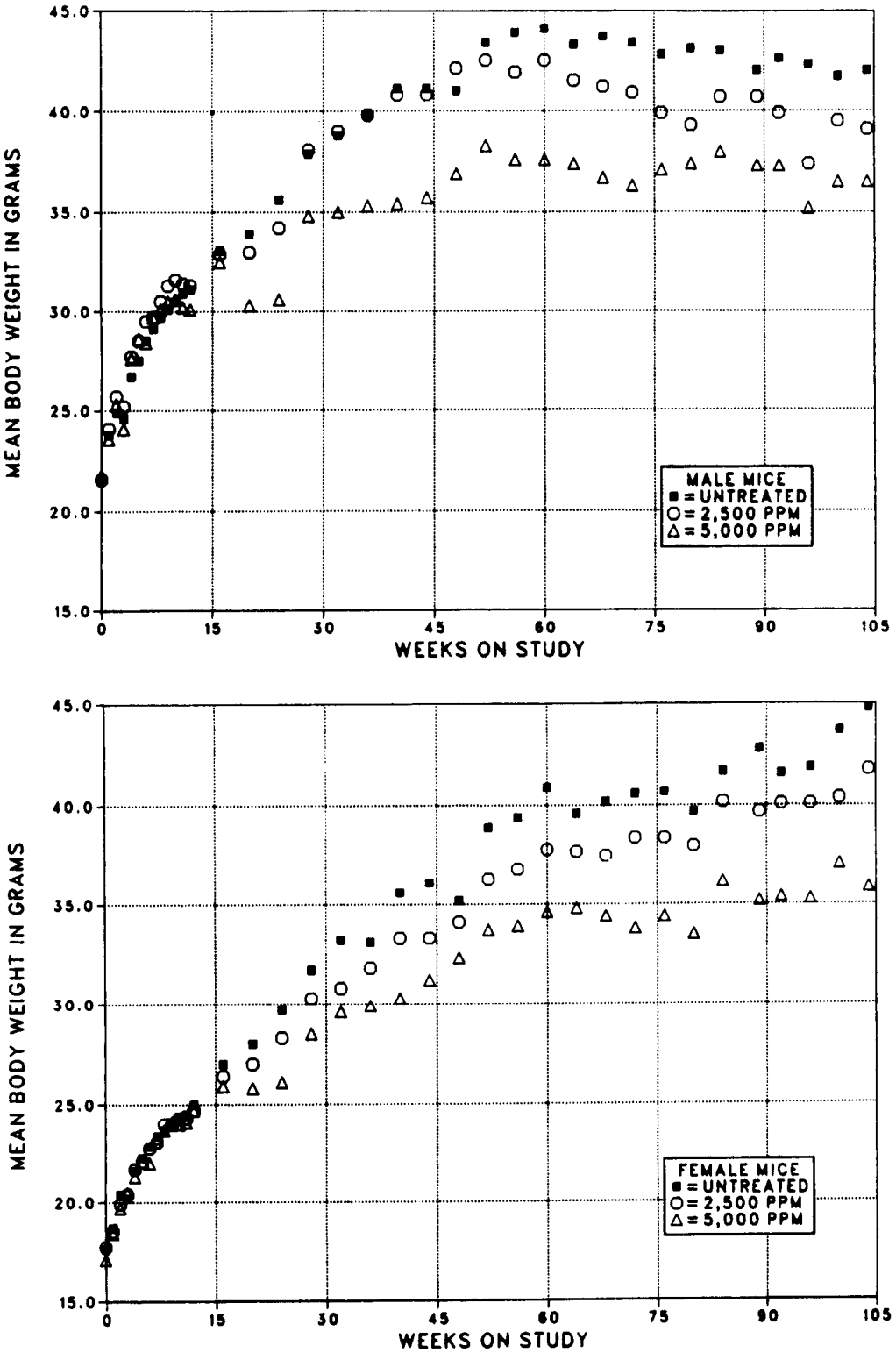


**FIGURE 1. GROWTH CURVES FOR MICE FED DIETS CONTAINING BORIC ACID FOR TWO YEARS**

## Survival

Estimates of the probabilities of survival for male and female mice fed diets containing boric acid at the concentrations used in these studies and for controls are shown in Table 8 and in the Kaplan and Meier curves in Figure 2. The survival of the high dose male group was significantly lower than that of the controls after week 63. The survival of the low dose male group was significantly lower than that of the control group after week 84 (except for week 101). No significant differences in survival were observed between any groups of female mice. During week 12, five high dose males and two low dose females drowned as a result of a clogged automatic water sipper tube.

## Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, subcutaneous tissue, spleen, testis, and lung.

Lesions in male mice are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male mice. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes). Historical incidences of tumors in control animals are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female mice are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female mice. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table B3 (footnotes). Findings on nonneoplastic lesions are summarized in Table B4.

TABLE 8. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF BORIC ACID

| | Control | 2,500 ppm | 5,000 ppm |
|---|---|---|---|
| **MALE** (a) | | | |
| Animals initially in study | 50 | 50 | 50 |
| Nonaccidental deaths before termination (b) | 9 | 20 | 23 |
| Accidentally killed | 0 | 0 | 5 |
| Killed at termination | 41 | 30 | 22 |
| Survival P values (c) | <0.001 | 0.020 | <0.001 |
| **FEMALE** (a) | | | |
| Animals initially in study | 50 | 50 | 50 |
| Nonaccidental deaths before termination (b) | 17 | 15 | 12 |
| Accidentally killed | 0 | 2 | 1 |
| Killed at termination | 32 | 33 | 37 |
| Died during termination period | 1 | 0 | 0 |
| Survival P values (c) | 0.366 | 0.997 | 0.410 |

(a) Terminal kill period: male, week 104-106; female, weeks 105-106
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

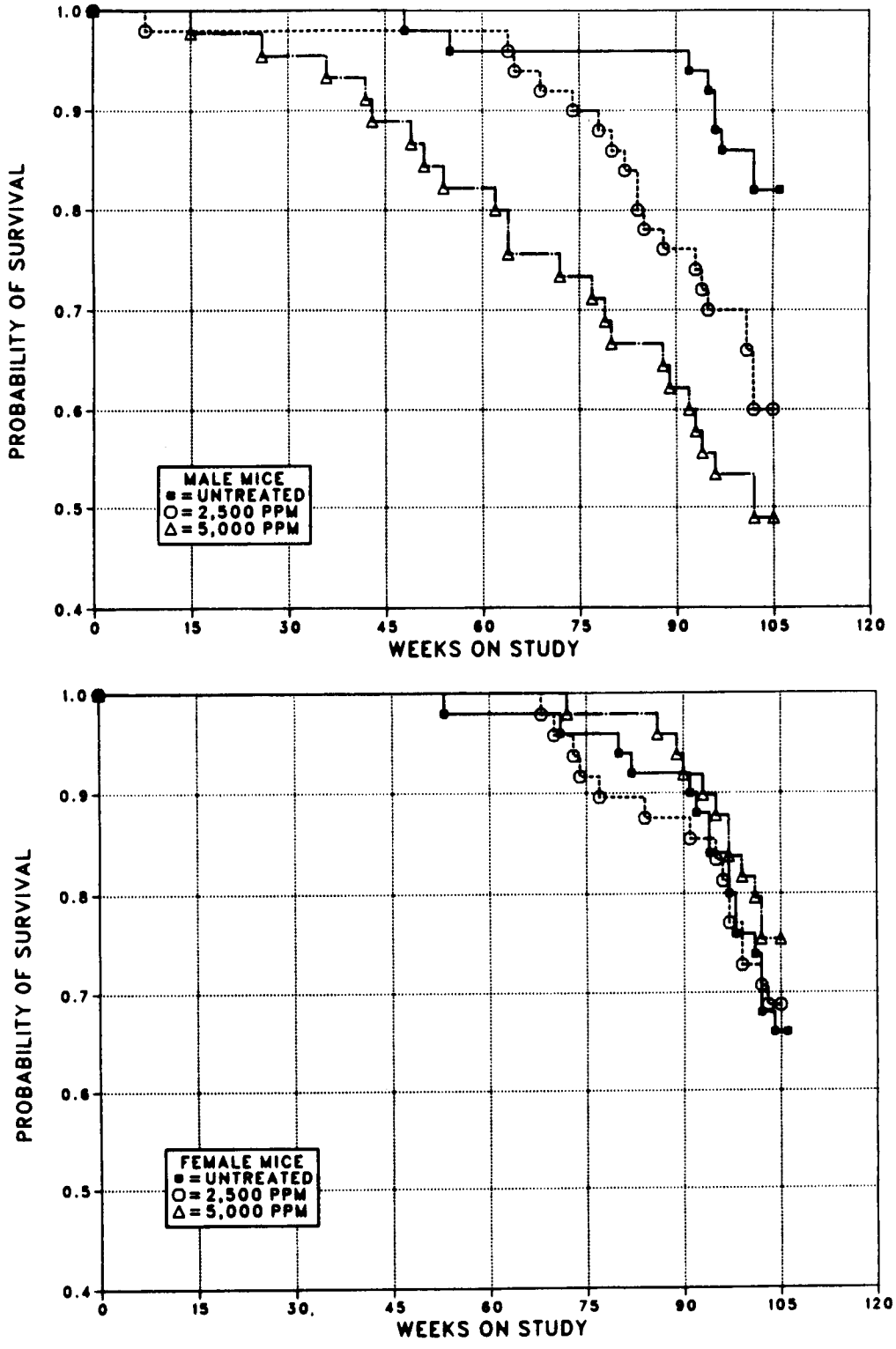


**FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING BORIC ACID FOR TWO YEARS**

*Liver:* Chronic inflammation was observed at increased incidences in low dose mice (male: control, 3/50; low dose, 9/50; high dose, 1/49; female: 16/50; 26/50; 9/50). Coagulative necrosis was observed in 3/50 control, 8/50 low dose, and 7/49 high dose male mice.

The incidence of hepatocellular carcinomas in low dose male mice was significantly greater than that in the controls by life table analysis (Table 9). Hepatocellular carcinomas and adenomas or carcinomas (combined) in male mice occurred with significant positive trends; the incidences of hepatocellular adenomas or carcinomas (combined) in dosed male mice were significantly greater than that in the controls by life table analysis. Hepatocellular carcinomas were observed in 3/50 control, 2/50 low dose, and 3/50 high dose female mice, and hepatocellular adenomas or carcinomas (combined) occurred with incidences of 5/50, 4/50, and 6/50 in these three groups.

**TABLE 9. ANALYSIS OF LIVER TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (a)**

| | Control | 2,500 ppm (b) | 5,000 ppm (b) |
|---|---|---|---|
| **Hepatocellular Adenoma (c)** | | | |
| Overall Rates | 11/50 (22%) | 9/50 (18%) | 8/49 (16%) |
| Adjusted Rates | 26.0% | 28.8% | 34.7% |
| Terminal Rates | 10/41 (24%) | 8/30 (27%) | 7/22 (32%) |
| Week of First Observation | 96 | 101 | 102 |
| Life Table Tests | P=0.277 | P=0.497 | P=0.320 |
| Incidental Tumor Tests | P=0.314 | P=0.551 | P=0.360 |
| **Hepatocellular Carcinoma (d)** | | | |
| Overall Rates | 5/50 (10%) | 12/50 (24%) | 8/49 (16%) |
| Adjusted Rates | 11.2% | 32.3% | 26.0% |
| Terminal Rates | 3/41 (7%) | 7/30 (23%) | 2/22 (9%) |
| Week of First Observation | 92 | 65 | 43 |
| Life Table Tests | P=0.035 | P=0.019 | P=0.056 |
| Incidental Tumor Tests | P=0.309 | P=0.139 | P=0.463 |
| **Hepatocellular Adenoma or Carcinoma (e)** | | | |
| Overall Rates | 14/50 (28%) | 19/50 (38%) | 15/49 (31%) |
| Adjusted Rates | 31.4% | 51.4% | 50.4% |
| Terminal Rates | 11/41 (27%) | 13/30 (43%) | 8/22 (36%) |
| Week of First Observation | 92 | 65 | 43 |
| Life Table Tests | P=0.023 | P=0.043 | P=0.038 |
| Incidental Tumor Tests | P=0.183 | P=0.211 | P=0.259 |

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) The estimated dose in milligrams per kilograms per day is given in Chapter III (Body Weights and Clinical Signs) and in Appendix I.
(c) Historical incidence at study laboratory (mean ± SD): 96/697 (14% ± 10%); historical incidence in NTP studies: 228/2,084 (11% ± 8%)
(d) Historical incidence at study laboratory (mean ± SD): 131/697 (19% ± 6%); historical incidence in NTP studies: 424/2,084 (20% ± 7%)
(e) Historical incidence at study laboratory (mean ± SD): 216/697 (31% ± 9%); historical incidence in NTP studies: 627/2,084 (30% ± 8%)

*Subcutaneous Tissue:* The incidence of fibromas, sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) in low dose male mice was significantly greater than that in controls (Table 10).

*Spleen:* Lymphoid depletion was observed at increased incidences in dosed male mice (male: control, 5/48; low dose, 11/49; high dose, 25/48; female: 3/49; 4/34; 4/50). Hematopoiesis was observed at increased incidences in dosed male mice (male: 3/48; 11/49; 10/48; female: 10/49; 11/34; 7/50).

*Testis:* Testicular atrophy and interstitial cell hyperplasia were observed at an increased incidence in high dose male mice (atrophy: control, 3/49; low dose, 6/50; high dose, 27/47; interstitial cell hyperplasia: 0/49; 0/50; 7/47). The testicular atrophy was characterized by variable loss of spermatogonia, primary and secondary spermatocytes, spermatids, and spermatozoa from the seminiferous tubules. The seminiferous tubules contained primarily Sertoli cells and variable numbers of spermatogonia. In some mice, there were accumulations of interstitial cells indicating hyperplasia.

*Lung:* The incidence of lung hemorrhage was increased in high dose female mice (control, 2/50; low dose, 5/50; high dose, 12/50).

At the end of the studies, 6/10 control mice had positive antibody titers for mouse hepatitis virus.

**TABLE 10. ANALYSIS OF SUBCUTANEOUS TISSUE TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID**

| | Control | 2,500 ppm | 5,000 ppm |
|---|---|---|---|
| **Fibroma** | | | |
| Overall Rates | 1/50 (2%) | 3/50 (6%) | 0/50 (0%) |
| **Fibrosarcoma** | | | |
| Overall Rates | 1/50 (2%) | 4/50 (8%) | 2/50 (4%) |
| **Sarcoma** | | | |
| Overall Rates | 0/50 (0%) | 2/50 (4%) | 0/50 (0%) |
| **Neurofibrosarcoma** | | | |
| Overall Rates | 0/50 (0%) | 1/50 (2%) | 0/50 (0%) |
| **Sarcoma, Fibrosarcoma, or Neurofibrosarcoma** | | | |
| Overall Rates | 1/50 (2%) | 7/50 (14%) | 2/50 (4%) |
| Adjusted Rates | 2.4% | 18.1% | 7.1% |
| Terminal Rates | 1/41 (2%) | 1/30 (3%) | 1/22 (5%) |
| Week of First Observation | 104 | 82 | 54 |
| Life Table Tests | P=0.184 | P=0.017 | P=0.331 |
| Incidental Tumor Tests | P=0.457 | P=0.084 | P=0.529 |
| **Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma (a)** | | | |
| Overall Rates | 2/50 (4%) | 10/50 (20%) | 2/50 (4%) |
| Adjusted Rates | 4.9% | 26.6% | 7.1% |
| Terminal Rates | 2/41 (5%) | 4/30 (13%) | 1/22 (5%) |
| Week of First Observation | 104 | 82 | 54 |
| Life Table Tests | P=0.239 | P=0.005 | P=0.493 |
| Incidental Tumor Tests | P=0.491 | P=0.026 | P=0.676 |

(a) Historical incidence at study laboratory (mean ± SD): 39/697 (6% ± 4%); historical incidence in NTP studies: 156/2,091 (7% ± 8%)

# IV. DISCUSSION AND CONCLUSIONS

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The NTP conducted 14-day, 13-week, and 2-year toxicology and carcinogenesis studies of boric acid in male and female B6C3F$_1$ mice; studies in Sprague-Dawley rats were conducted by Weir and Fisher (1972). The short-term studies indicated that the major effect of boric acid at high doses was testicular atrophy and degeneration. Initial 14-day studies were conducted at doses that did not cause any observable toxic effects, and studies were repeated at tenfold higher doses, ranging from 6,200 to 100,000 ppm. There was over 80% mortality in both sexes of mice fed 100,000 ppm boric acid in the diet and 60% mortality in males fed 50,000 ppm of the chemical; one male in the 25,000-ppm group died. The main clinical sign associated with these high doses was lethargy. The spleen, liver, and renal medullae were discolored; hyperkeratosis and dysplasia of the forestomach constituted the principal histopathologic findings. The five doses selected for the 13-week studies ranged between 1,200 and 20,000 ppm. At these doses, mice displayed nervousness and, at the high doses, were thin, haunchy, and dehydrated; they had foot lesions and dry, scaly tails. Gross pathologic and histopathologic findings similar to those associated with the 14-day studies were observed in the 13-week studies. The affected organs were identified as the stomach and spleen in each sex and the testis in males. There were increases in the incidences of hyperkeratosis and/or acanthosis in the stomach and extramedullary hematopoiesis of the spleen in each sex and degeneration or atrophy of the seminiferous tubules of the testis in males.

Mice in the 2-year studies were fed diets containing 2,500 or 5,000 ppm boric acid because of the mortality, depressed weight gain, and histopathologic lesions seen at the higher doses in the 13-week studies. By comparison with controls, there were fewer surviving high dose male mice after week 63 and fewer surviving low dose male mice after week 84. Two female and five male mice from the high dose groups accidentally drowned during week 12, so the differences in survival of male mice were not entirely attributable to the chemical. At terminal kill, 41 control, 30 low dose, and 22 high dose male mice and 33 control, 33 low dose, and 37 high dose female mice were available for histologic examination; these numbers of female mice were considered sufficient to detect the toxicologic effects in mice, but the lower numbers of male mice may have reduced the sensitivity of the study.

Administration of boric acid caused a dose-related reduction in body weight gain which was evident after about week 30 in both male and female mice. Except for bite wounds in male mice, no clinical signs were observed in the 2-year studies.

Administration of boric acid to male mice caused testicular atrophy and interstitial cell hyperplasia. The testicular atrophy was characterized by variable loss of spermatogonia, primary and secondary spermatocytes, spermatids, and spermatozoa from the seminiferous tubules. The seminiferous tubules contained primarily Sertoli cells and variable numbers of spermatogonia. In some mice, there were accumulations of interstitial cells, indicating hyperplasia. This toxic effect has been well documented in other studies (Weir and Fisher, 1972; Silaev et al., 1977; Krasovskii et al., 1976). The doses of boric acid used in these studies were either very high (1,000 mg/kg per day for 14 or 90 days) or were administered for long intervals (6 mg/liter in the drinking water for 6 months). It is unlikely that the levels of boric acid found in cosmetics (0.1%-5%; CTFA, 1983) or as nuisance dust levels in occupational conditions (10 mg/m$^3$ $\simeq$ 1 mg/kg per day in humans) would pose a threat of reproductive toxicity to humans. Although Silaev et al. (1977) hypothesized that boric acid induced histologic abnormalities in rat testes through interference with the meiotic division of spermatocytes, the uniformly negative results of NTP genotoxicity tests suggest that the observed nonneoplastic effects in the testis may not be genetically mediated.

There were dose-related increased incidences of splenic lymphoid depletion in male mice given boric acid. This lesion is often associated with stress and debilitation and reflects the increased mortality in these groups of male mice. There were slightly increased incidences of other nonneoplastic lesions in male and female mice which were not always consistently dose related or found in both sexes and are not believed to have been caused by the administration of boric acid.

There were slightly increased incidences of subcutaneous tissue tumors (fibromas, fibrosarcomas, sarcomas, or neurofibrosarcomas, combined) in low dose male mice. Since there was no corresponding increase in high dose male mice, and since the incidences of these neoplasms are highly variable in the historical controls (Appendix A, Table A4a), they are not believed to have been caused by administration of boric acid. There were marginally increased incidences of hepatocellular carcinomas in low dose male mice and of hepatocellular adenomas or carcinomas (combined) in dosed male mice. These neoplasms were marginally significant by the life table test only and were within the historical control range. Moreover, these increases were not significant by the incidental tumor test, which is probably more appropriate in this instance because there was no indication that these tumors were the cause of death. Therefore, the increases are not believed to be related to the administration of boric acid.

The feed consumption values for the control and dosed groups were higher than the normal value of approximately 4 g per mouse per day (Appendix I). The higher than normal value for the control group is probably due to feeders that did not prevent spillage. Higher feed consumption values for the dosed groups may be due to decreased palatability of the formulated diets, which generally results in more feed spillage. Therefore, a better approximation of boric acid consumption for the male and female mice at the 2,500- and 5,000-ppm concentrations would be 275 and 550 mg/kg per day. By comparison, Weir and Fisher (1972) fed Sprague-Dawley rats 67, 200, or 669 mg/kg per day boron equivalents for 2 years. Their findings that boric acid was not carcinogenic in rats are confirmed by the present studies in male and female $B6C3F_1$ mice.

In a variety of genotoxicity tests with prokaryotic and eukaryotic cells, boric acid was found to be uniformly nonmutagenic. Boric acid also did not induce sister-chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells (Appendix C).

The experimental and tabulated data for the NTP Technical Report on boric acid were examined for accuracy, consistency, and compliance with Good Laboratory Practice requirements. As summarized in Appendix K, the audit revealed no major problems with the conduct of the studies or with the collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

*Conclusions:* Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenicity** of boric acid at doses of 2,500 or 5,000 ppm for male or female $B6C3F_1$ mice. Testicular atrophy and interstitial cell hyperplasia were observed in high dose male mice. The decrease in survival of dosed male mice may have reduced the sensitivity of this study.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 8.

# V. REFERENCES

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1. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons Inc., pp. 362-365.

2. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

3. Boorman, G.; Montgomery, C., Jr.; Eustis, S.; Wolfe, M.; McConnell, E.; Hardisty, J. (1985) Quality assurance in pathology for rodent carcinogenicity studies. Milman, H.; Weisburger, E., Eds.: Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications, pp. 345-357.

4. Boyland, E.; Roe, F.; Mitchley, B. (1966) Test of certain constituents of spermicides for carcinogenicity in genital tract of female mice. Br. J. Cancer 20:184-189.

5. Clive, D.; Johnson, K.; Spector, J.; Batson, A.; Brown, M. (1979) Validation and characterization of the L5178Y/TK$^{+/-}$ mouse lymphoma mutagen assay system. Mutat. Res. 59:61-108.

6. Cosmetic, Toiletry, and Fragrance Association (CTFA) (1983) Cosmetic Ingredient Review. Final Report of the Safety Assessment for Sodium Borate and Boric Acid.

7. Cox, D. (1972) Regression models and life tables. J. R. Stat. Soc. B34:187-220.

8. Dani, H.; Saini, H.; Allag, I.; Singh, B.; Sareen, K. (1971) Effect of boron toxicity on protein and nucleic acid contents of rat tissues. Res. Bull. Punjab Univ. 22:229-235.

9. Datta, A.; Randolph, B.; Rosner, J. (1983) Detection of chemicals that stimulate Tn*9* transposition in *Escherichia coli* K12. Mol. Gen. Genet. 189:245-250.

10. Demerec, M.; Bertani, G.; Flint, J. (1951) A survey of chemicals for mutagenic action on E. coli. Am. Nat. 85:119-136.

11. Draize, J.; Kelley, E. (1959) The urinary excretion of boric acid preparations following oral administration and topical applications to intact and damaged skin of rabbits. Toxicol. Appl. Pharmacol. 1:267-276.

12. Federal Register (Fed. Regist.) (1969) 34:14651, Sept. 20.

13. Food and Drug Administration (FDA) (1978) Monograph on Borax, Boric Acid, and Borates. NTIS PB-287 761.

14. Food and Drug Administration (FDA) (1980a) OTC Ophthalmic Report. Proposed monograph. Fed. Regist. 45:30029-30030.

15. Food and Drug Administration (FDA) (1980b) OTC Anorectal Report. Proposed monograph. Fed. Regist. 45:35659-35660.

16. Galloway, S.; Bloom, A.; Resnick, M.; Margolin, B.; Nakamura, F.; Archer, P.; Zeiger, E. (1985) Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ. Mutagen. 7:1-51.

17. Gart, J.; Chu, K.; Tarone, R. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62:957-974.

18. Goldbloom, R.; Goldbloom, A. (1953) Boric acid poisoning: Report of four cases and a review of 109 cases from the world literature. J. Pediatr. 43:631-643.

19. Haseman, J. (1984) Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ. Health Perspect. 58:385-392.

20. Haseman, J.; Huff, J.; Boorman, G. (1984) Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12:126-135.

21. Haseman, J.; Huff, J.; Rao, G.; Arnold, J.; Boorman, G.; McConnell, E. (1985) Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)$F_1$ (B6C3$F_1$) mice. J. Natl. Cancer Inst. 75:975-984.

22. Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W.; Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl. 1:3-142.

23. Iyer, V.; Szybalski, W. (1958) Two simple methods for the detection of chemical mutagens. Appl. Microbiol. 6:23-29.

24. John, M.; Chuah, H.; Neufeld, J. (1975) Anal. Lett. 8:559-568.

25. Johnstone, D.; Basila, N.; Glaser, J. (1955) A study of boric acid absorption in infants from the use of baby powders. J. Pediatr. 46:160-167.

26. Kaplan, E.; Meier, P. (1958) Nonparametric estimation of incomplete observations. J. Am. Stat. Assoc. 53:457-481.

27. Krasovskii, G.; Varshavskaya, S.; Borisov, A. (1976) Toxic and gonadotropic effects of cadmium and boron relative to standards for these substances in drinking water. Environ. Health Perspect. 13:69-75.

28. Kunkel, A. (1950) Literature Survey on Toxicity of Boric Acid and Sodium Tetraborate (Borax). Medical Division Special Report No. 2. Army Chemical Center, Maryland.

29. Lee, I.; Sherins, R.; Dixon, R. (1978) Evidence for induction of germinal aplasia in male rats by environmental exposure to boron. Toxicol. Appl. Pharmacol. 45:577-590.

30. Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J. (1974) Carcinogenesis Bioassay Data System. Comput. Biomed. Res. 7:230-248.

31. Mannsville Chemical Products Corp. (1984) Chemical Products Synopsis--Boric Acid. Cortland, NY, October. 2 p.

32. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

33. Maronpot, R.; Boorman, G. (1982) Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Toxicol. Pathol. 10:71-80.

34. McConnell, E.; Solleveld, H.; Swenberg, J.; Boorman, G. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. 76:283-289.

35. Merck Index, 9th ed. (1973) Windholz, M., Ed. Rahway, NJ: Merck and Co., p. 173.

36. Mulinos, M.; Connant, C.; Hauser, E. (1953) The toxicity of boric acid and the clinical implications of the use of borated baby powders. Bull. N.Y. Med. Coll. 16:92-101.

37. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Technical Report No. 1. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

38. National Institutes of Health (NIH) (1978) NIH Specification, NIH-11-133f, November 1.

39. Ogawa, S.; Toyoda, M.; Tonogai, Y.; Ito, Y.; Iwaida, M. (1979) Colorimetric determination of boric acid in prawns, shrimp, and salted jellyfish by chelate extraction with 2-ethyl-1,3-hexanediol. J. Off. Anal. Chem. 62:610-614.

40. Pfeiffer, C.; Jenney, E. (1950) The pharmacology of boric acid and boron compounds. Bull. Natl. Form. Comm. 18:57-80.

41. Ploquin, J. (1966) Boron in nutrition. Bull. Acad. Natl. Med. 150:509-512.

42. Roe, D.; McCormick, D.; Lin, R.-T. (1972) Effects of riboflavin on boric acid toxicity. J. Pharm. Sci. 61:1081-1085.

43. Sadtler Standard Spectra, IR No. 2700. Philadelphia: Sadtler Research Laboratories.

44. Schuppli, R.; Seiler, H.; Schneeberger, R.; Niggli, H.; Hoffmann, K. (1971) On the toxicity of boric acid. Dermatologica (Basel) 143:227-234.

45. Silaev, A.; Kasparov, A.; Korolev, V.; Nebstrueva, V. (1977) Electron-microscopic investigation of the effect of boric acid on the seminiferous tubules of albino rats. Bull. Exp. Biol. Med. (USSR) 83:588-591.

46. Swate, T.; Weed, J. (1974) Boric acid treatment of vulvo vaginal candidiasis. Obstet. Gynecol. 43:893-895.

# V. REFERENCES

47. Szybalski, W. (1958) Special microbiological systems. II. Observations on chemical mutagenesis in microorganisms. Ann. N.Y. Acad. Sci. 76:475-489.

48. Tarone, R. (1975) Tests for trend in life table analysis. Biometrika 62:679-682.

49. Thorpe, V. (1978) Microcolorimetric method for determining boron in fertilizers. J. Assoc. Off. Anal. Chem. 61:894-897.

50. The United States Pharmacopeia (USP) (1965) 19th rev. New York: The United States Pharmacopeial Convention, Inc., p. 82.

51. Vignec, A.; Ellis, R. (1954) Inabsorbability of boric acid in infant powder. Am. J. Dis. Child. 88:72-80.

52. Weir, R., Jr.; Fisher, R. (1972) Toxicologic studies on borax and boric acid. Toxicol. Appl. Pharmacol. 23:351-364.

53. Weser, U. (1967) Stimulation of rat liver RNA synthesis by borate. Proc. Soc. Exp. Biol. Med. 126:669-671.

54. Weser, U. (1968) Effect of borate and germanate on RNA biosynthesis. Hoppe-Seyler's Z. Physiol. Chem. 349:989-994.

55. Wolf, B. (1971) The determination of boron in soil extracts, plant materials, composts, manures, water and nutrient solutions. Communications in Soil Science and Plant Analysis, Vol. 2. New York: Marcel Dekker, Inc., pp. 363-374.

# APPENDIX A

# SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID

**TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID**

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *Subcutaneous tissue | (50) | (50) | (50) |
| Sarcoma, NOS | | 2 (4%) | |
| Fibroma | 1 (2%) | 3 (6%) | |
| Fibrosarcoma | 1 (2%) | 4 (8%) | 2 (4%) |
| Neurofibrosarcoma | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #Lung | (50) | (50) | (50) |
| Hepatocellular carcinoma, metastatic | 2 (4%) | 7 (14%) | 1 (2%) |
| Mixed hepato/cholangioca, metastatic | | 1 (2%) | |
| Alveolar/bronchiolar adenoma | 10 (20%) | 8 (16%) | 4 (8%) |
| Alveolar/bronchiolar carcinoma | 1 (2%) | 3 (6%) | |
| Sarcoma, NOS, metastatic | | 2 (4%) | |
| HEMATOPOIETIC SYSTEM | | | |
| *Multiple organs | (50) | (50) | (50) |
| Malignant lymphoma, undiffer type | 1 (2%) | | 1 (2%) |
| Malignant lymphoma, lymphocytic type | | | 1 (2%) |
| Malignant lymphoma, mixed type | 1 (2%) | 1 (2%) | |
| #Mesenteric lymph node | (43) | (32) | (42) |
| Malignant lymphoma, undiffer type | | 1 (3%) | |
| #Renal lymph node | (43) | (32) | (42) |
| Malignant lymphoma, undiffer type | 1 (2%) | | |
| #Lymph node of upper extremity | (43) | (32) | (42) |
| Neurofibrosarcoma, invasive | | 1 (3%) | |
| #Inguinal lymph node | (43) | (32) | (42) |
| Sarcoma, NOS, metastatic | | 1 (3%) | |
| #Peyer's patch | (50) | (12) | (48) |
| Malignant lymphoma, undiffer type | 1 (2%) | | |
| CIRCULATORY SYSTEM | | | |
| *Multiple organs | (50) | (50) | (50) |
| Hemangiosarcoma | 1 (2%) | | |
| #Spleen | (48) | (49) | (48) |
| Hemangioma | 2 (4%) | | |
| #Heart | (50) | (12) | (50) |
| Alveolar/bronchiolar carcinoma, metastatic | | 1 (8%) | |
| #Liver | (50) | (50) | (49) |
| Hemangioma | 2 (4%) | | |
| Hemangiosarcoma | 1 (2%) | 1 (2%) | |
| Hemangiopericytoma, NOS | | 1 (2%) | |
| DIGESTIVE SYSTEM | | | |
| #Salivary gland | (49) | (49) | (47) |
| Sarcoma, NOS, unclear primary or metastatic | | 1 (2%) | |
| #Liver | (50) | (50) | (49) |
| Hepatocellular adenoma | 11 (22%) | 9 (18%) | 8 (16%) |
| Hepatocellular carcinoma | 5 (10%) | 12 (24%) | 8 (16%) |
| Mixed hepato/cholangiocarcinoma | | 1 (2%) | |
| Sarcoma, NOS | 1 (2%) | | |
| Sarcoma, NOS, metastatic | | 1 (2%) | |

**TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)**

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| DIGESTIVE SYSTEM (Continued) | | | |
| #Pancreas | (49) | (48) | (45) |
| Sarcoma, NOS, unclear primary or metastatic | | 1 (2%) | |
| #Forestomach | (49) | (50) | (49) |
| Squamous cell papilloma | 2 (4%) | 1 (2%) | 4 (8%) |
| #Jejunum | (50) | (12) | (48) |
| Adenocarcinoma, NOS | 1 (2%) | | |
| URINARY SYSTEM | | | |
| None | | | |
| ENDOCRINE SYSTEM | | | |
| #Pituitary intermedia | (35) | (9) | (47) |
| Adenoma, NOS | 1 (3%) | | |
| #Anterior pituitary | (35) | (9) | (47) |
| Adenoma, NOS | | | 1 (2%) |
| #Adrenal | (50) | (11) | (48) |
| Cortical adenoma | | 1 (9%) | |
| #Adrenal medulla | (50) | (11) | (48) |
| Pheochromocytoma | 1 (2%) | | |
| #Thyroid | (44) | (12) | (48) |
| C-cell carcinoma | 1 (2%) | | |
| REPRODUCTIVE SYSTEM | | | |
| None | | | |
| NERVOUS SYSTEM | | | |
| None | | | |
| SPECIAL SENSE ORGANS | | | |
| *Harderian gland | (50) | (50) | (50) |
| Adenoma, NOS | 3 (6%) | 1 (2%) | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | |
| None | | | |
| BODY CAVITIES | | | |
| *Mediastinum | (50) | (50) | (50) |
| Sarcoma, NOS, unclear primary or metastatic | | 1 (2%) | |
| ALL OTHER SYSTEMS | | | |
| *Multiple organs | (50) | (50) | (50) |
| Sarcoma, NOS, unclear primary or metastatic | | | 1 (2%) |
| Mesothelioma, NOS | | 1 (2%) | |

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| Animals initially in study | 50 | 50 | 50 |
| Natural death | 7 | 13 | 15 |
| Moribund sacrifice | 2 | 7 | 8 |
| Terminal sacrifice | 41 | 30 | 22 |
| Accidentally killed, nda | | | 5 |
| TUMOR SUMMARY | | | |
| Total animals with primary tumors** | 31 | 37 | 23 |
| Total primary tumors | 49 | 54 | 31 |
| Total animals with benign tumors | 23 | 22 | 16 |
| Total benign tumors | 33 | 23 | 18 |
| Total animals with malignant tumors | 13 | 23 | 11 |
| Total malignant tumors | 16 | 26 | 12 |
| Total animals with secondary tumors## | 2 | 10 | 1 |
| Total secondary tumors | 2 | 14 | 1 |
| Total animals with tumors uncertain--benign or malignant | | 2 | |
| Total uncertain tumors | | 2 | |
| Total animals with tumors uncertain--primary or metastatic | | 2 | 1 |
| Total uncertain tumors | | 3 | 1 |

• Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
## Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

## TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID: UNTREATED CONTROL

| ANIMAL NUMBER | 0016 | 0006 | 0447 | 0333 | 0139 | 0488 | 0122 | 0077 | 0444 | 0011 | 0033 | 0044 | 0055 | 0088 | 0099 | 0110 | 0111 | 0155 | 0177 | 0188 | 0199 | 0220 | 0221 | 0222 | 0224 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 048 | 055 | 092 | 095 | 096 | 096 | 097 | 102 | 102 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma, metastatic | | | X | X | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma | | | | | | | | | X | | | X | X | | | | | | | X | | | X | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Trachea | + | − | − | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + |
| Spleen | + | − | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Lymph nodes | + | − | + | − | + | + | − | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | − | − | − | + | + | − | − | + | + | + | − | + | + | + | + | + | − | + | + | + | + | + | + | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | X | | | | | | | | | | | | | X | | | | X | | |
| Hepatocellular carcinoma | | | X | X | | | | | | | | | | | X | | | | X | | | | | | |
| Sarcoma, NOS | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangioma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | N | + | + | N | N | N | + | + | + | N | + | + | + | N | + | + | + | + | + | + | + | + | + | + |
| Pancreas | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | − | − | + | + | − | − | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | − |
| Stomach | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Large intestine | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | − | + | + | − | + | + | − | − | + | + | + | + | + | − | − | + | + | + | + | + | + | + | − | + | − |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Thyroid | + | − | − | + | + | − | + | − | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid | + | − | − | + | + | − | − | − | − | − | − | + | − | + | − | + | − | − | − | − | + | + | − | + | + |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | N | + | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | | X | | | | | | | | | | X | | | | | | | | | |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Hemangiosarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Malignant lymphoma, mixed type | | | | | X | | | | | | | | | | | | | | | | | | | | |

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

## TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

| ANIMAL NUMBER | 025 | 002 | 014 | 023 | 026 | 027 | 028 | 029 | 030 | 031 | 032 | 034 | 035 | 036 | 037 | 038 | 039 | 040 | 041 | 042 | 043 | 045 | 046 | 049 | 050 | TOTAL: |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 105 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | TISSUES / TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | *50 |
| Fibroma | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| Fibrosarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular carcinoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Alveolar/bronchiolar adenoma | | | X | | | | | X | | | X | | | | | | X | | X | | | | | | 10 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | 46 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Hemangioma | | | | | | | | | | | | | | | | X | | | | | | | | | | 2 |
| Lymph nodes | + | + | + | – | + | + | + | + | + | – | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | 43 |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Thymus | + | + | – | + | + | + | + | – | + | + | + | – | + | + | – | – | – | + | + | – | + | – | + | + | + | 35 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | | | | | | | | | X | | | | | X | X | X | X | | | X | | X | X | | | 11 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 5 |
| Sarcoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangioma | | | | | | | | | | | | | | | | X | | | | | | | | | | 2 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder & common bile duct | + | + | N | + | + | N | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | *50 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Esophagus | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | 42 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Squamous cell papilloma | | | | X | | | | | | | | | | | | X | | | | | | | | | | 2 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | – | + | + | – | – | + | + | – | + | + | – | + | + | + | + | + | + | + | + | + | + | – | + | – | + | 35 |
| Adenoma, NOS | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | 44 |
| C-cell carcinoma | | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid | – | + | + | – | – | + | + | – | + | + | + | + | – | + | – | + | + | – | + | – | – | – | – | + | – | 23 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Testis | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Prostate | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Adenoma, NOS | | X | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Malignant lymphoma, mixed type | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

* Animals necropsied

## TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID: LOW DOSE

| ANIMAL NUMBER | 0016 | 0046 | 0036 | 0047 | 0024 | 0030 | 0034 | 0010 | 0001 | 0043 | 0009 | 0045 | 0021 | 0008 | 0019 | 0012 | 0033 | 0018 | 0025 | 0049 | 0002 | 0003 | 0004 | 0005 | 0017 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 008 | 064 | 065 | 069 | 074 | 078 | 080 | 082 | 084 | 084 | 085 | 088 | 093 | 094 | 095 | 101 | 101 | 102 | 102 | 102 | 104 | 104 | 104 | 104 | 104 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | + | + | + | + | + | + | + | + | + | + | + | N | + | N | + | N | + | + | N | + | N | N | + | N | N |
| Sarcoma, NOS | | | | | | | | X | | | | | | | X | | | | | | | | | | |
| Fibroma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Fibrosarcoma | | | | | | | | | | | X | | | | | | | X | | X | | | | | |
| Neurofibrosarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma, metastatic | | | | | | | | X | | X | | | | | | | | X | | | | | | X | |
| Mixed hepato/cholangiocarcinoma, metastatic | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma | | | | | | X | X | | | | | | | | | | | | | | | X | | X | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | X | | | | | | | | X | | | | | |
| Sarcoma, NOS, metastatic | | | | | | X | | X | | | | | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | + | + | + | + | + | + | + | + | − | − | + | + | + | + | + | − | + | + | + | − | + | + | + | − | + |
| Sarcoma, NOS, metastatic | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Neurofibrosarcoma, invasive | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | | X | | | | |
| Thymus | + | − | + | − | − | + | + | − | − | − | − | − | − | − | − | + | − | + | − | − | − | − | − | − | − |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Alveolar/bronchiolar carcinoma, metastatic | | | | | | | | | | | | X | | | | | | | | | | | | | |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma, NOS, unclear primary or metastatic | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Hepatocellular carcinoma | | | X | | | | | X | X | X | | | | | | | | X | | | | | | X | |
| Mixed hepato/cholangiocarcinoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Sarcoma, NOS, metastatic | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiopericytoma, NOS | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | N | + | + | + | N | + | N | + | N | + | + | + | N | N | + | N | + | + | + | + | + | + | + | N |
| Pancreas | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + |
| Sarcoma, NOS, unclear primary or metastatic | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Small intestine | + | + | + | + | + | + | + | + | − | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | − | + | + | + | + | + | + | + | − | + | + | + | − | − | − | + | + | − | + | − | − | − | − | − | − |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | − | + | + | + | − | + | − | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Adrenal | + | + | + | + | + | + | + | − | + | − | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Cortical adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Parathyroid | + | − | + | + | + | − | − | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | − | + | + | + | + | + | + | − | − | − | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **BODY CAVITIES** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mediastinum | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Sarcoma, NOS, unclear primary or metastatic | | | | | | X | | | | | | | | | | | | | | | | | | | |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Mesothelioma, NOS | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Malignant lymphoma, mixed type | | | | | | | | | | | | | | | | | | | | | | X | | | |

## TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

| ANIMAL NUMBER | 00 06 | 00 07 | 01 11 | 01 13 | 01 14 | 01 15 | 02 20 | 02 22 | 02 23 | 02 26 | 02 27 | 02 28 | 02 29 | 03 31 | 03 32 | 03 35 | 03 37 | 03 38 | 03 39 | 04 40 | 04 41 | 04 42 | 04 44 | 04 48 | 05 50 | TOTAL: TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | N | + | + | + | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Sarcoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Fibroma | | X | | X | | | | | | | | | | | | | | | | | | | | | | 3 |
| Fibrosarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Neurofibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular carcinoma, metastatic | | | | X | | | | | | | | | | | | | | | | | | X | | | X | 7 |
| Mixed hepato/cholangiocarcinoma, meta | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | X | | | | | | X | X | X | | | | 8 |
| Alveolar/bronchiolar carcinoma | | | | | X | | | | | | | | | | | | | | | | | | | | | 3 |
| Sarcoma, NOS, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Trachea | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 12 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 12 |
| Spleen | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Lymph nodes | + | + | – | + | + | + | + | + | – | – | + | + | – | – | + | – | – | – | – | + | – | – | – | – | + | 32 |
| Sarcoma, NOS, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Neurofibrosarcoma, invasive | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | – | – | – | – | + | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 7 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 12 |
| Alveolar/bronchiolar carcinoma, metast | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Sarcoma, NOS, unclear primary or meta | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | X | | | | X | X | | | | X | X | X | X | | | | | | | | | X | | | | 9 |
| Hepatocellular carcinoma | X | | | X | | | | X | | | | | | | | | | | | | | X | | X | X | 12 |
| Mixed hepato/cholangiocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma, NOS, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangiosarcoma | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| Hemangiopericytoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder & common bile duct | + | + | + | N | + | + | N | N | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | N | + | *50 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Sarcoma, NOS, unclear primary or meta | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Esophagus | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 12 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Small intestine | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | + | – | – | – | 12 |
| Large intestine | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 12 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | – | – | – | – | – | – | – | + | – | – | – | + | + | + | – | – | – | – | – | – | – | + | – | – | + | 19 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 9 |
| Adrenal | – | – | – | – | – | – | – | – | + | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 11 |
| Cortical adenoma | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| Thyroid | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 12 |
| Parathyroid | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 7 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Prostate | – | – | – | + | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 9 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Adenoma, NOS | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| **BODY CAVITIES** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mediastinum | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Sarcoma, NOS, unclear primary or meta | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Mesothelioma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Malignant lymphoma, mixed type | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

* Animals necropsied

## TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID: HIGH DOSE

| ANIMAL NUMBER | 0016 | 0017 | 0018 | 0019 | 0020 | 0043 | 0010 | 0002 | 0050 | 0008 | 0041 | 0003 | 0007 | 0005 | 0035 | 0046 | 0027 | 0031 | 0014 | 0048 | 0034 | 0037 | 0012 | 0044 | 0032 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 013 | 013 | 013 | 013 | 013 | 015 | 026 | 036 | 042 | 043 | 049 | 051 | 054 | 062 | 064 | 064 | 072 | 077 | 079 | 080 | 088 | 089 | 092 | 093 | 094 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | N | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + |
| Fibrosarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph nodes | − | + | − | − | + | + | − | − | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | − | + | − | − | + | − | − | − | − | − | − | + | + | − | + | + | + | + | − | − | − | − | − | − | − |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | − | − | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | | | | | | X | | | | | | | X | | | | | X | X | | X |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | + | + | + | N | + | N | + | N | + | + | + | + | + | + | + | N | N | + | + | + | + | N | + | + |
| Pancreas | − | − | + | + | + | + | − | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Small intestine | − | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + |
| Large intestine | − | + | + | − | + | − | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | − | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma, NOS | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid | + | − | − | − | − | + | − | − | + | + | + | − | + | − | − | + | − | − | − | + | − | + | − | − | + |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N |
| Testis | + | + | + | + | + | − | + | + | + | + | + | − | + | + | − | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | − |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Sarcoma, NOS, unclear primary or metastatic | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | | | | | | |
| Malignant lymphoma, lymphocytic type | | | | | | | | | | | | | | | | | | | | | | | X | | |

## TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

| ANIMAL NUMBER | 029 | 047 | 049 | 001 | 004 | 006 | 009 | 011 | 013 | 015 | 033 | 021 | 022 | 023 | 024 | 025 | 026 | 028 | 030 | 036 | 038 | 039 | 040 | 042 | 045 | TOTAL: |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 096 | 102 | 102 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | *50 |
| Fibrosarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | | 2 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular carcinoma, metastatic | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Alveolar/bronchiolar adenoma | X | | | | X | | | | | X | | | | | | | X | | | | | | | | | 4 |
| Trachea | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | 48 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | 48 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | 48 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | – | + | + | + | + | + | 42 |
| Thymus | – | – | – | + | – | + | – | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | 27 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Hepatocellular adenoma | | X | | | X | | | | | | X | | X | | | | X | X | X | | | X | | | | 8 |
| Hepatocellular carcinoma | X | | | | | | | X | | | | | | | | | | | | | | X | | | | 8 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Gallbladder & common bile duct | N | + | + | + | + | + | N | + | + | + | + | N | + | + | + | + | + | + | N | + | + | N | + | + | N | *50 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 45 |
| Esophagus | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | – | + | + | + | + | 47 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Squamous cell papilloma | | | | X | | | | | | | X | | | | | | | | | X | | | | | | 4 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | 47 |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Thyroid | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | 48 |
| Parathyroid | + | + | + | – | – | – | + | + | + | + | + | + | + | – | – | + | + | – | + | – | + | – | – | – | – | 24 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | + | + | N | N | N | + | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Testis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | 46 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Adenoma, NOS | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Sarcoma, NOS, unclear primary or meta | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| Malignant lymphoma, lymphocytic type | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID

| | Control | 2,500 ppm | 5,000 ppm |
|---|---|---|---|
| **Subcutaneous Tissue: Fibroma** | | | |
| Overall Rates (a) | 1/50 (2%) | 3/50 (6%) | 0/50 (0%) |
| Adjusted Rates (b) | 2.4% | 10.0% | 0.0% |
| Terminal Rates (c) | 1/41 (2%) | 3/30 (10%) | 0/22 (0%) |
| Week of First Observation | 104 | 104 | |
| Life Table Tests (d) | P=0.580N | P=0.201 | P=0.624N |
| Incidental Tumor Tests (d) | P=0.580N | P=0.201 | P=0.624N |
| Cochran-Armitage Trend Test (d) | P=0.378N | | |
| Fisher Exact Test (d) | | P=0.309 | P=0.500N |
| **Subcutaneous Tissue: Fibrosarcoma** | | | |
| Overall Rates (a) | 1/50 (2%) | 4/50 (8%) | 2/50 (4%) |
| Adjusted Rates (b) | 2.4% | 11.5% | 7.1% |
| Terminal Rates (c) | 1/41 (2%) | 1/30 (3%) | 1/22 (5%) |
| Week of First Observation | 104 | 85 | 54 |
| Life Table Tests (d) | P=0.205 | P=0.113 | P=0.331 |
| Incidental Tumor Tests (d) | P=0.405 | P=0.262 | P=0.529 |
| Cochran-Armitage Trend Test (d) | P=0.406 | | |
| Fisher Exact Test (d) | | P=0.181 | P=0.500 |
| **Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma** | | | |
| Overall Rates (a) | 1/50 (2%) | 7/50 (14%) | 2/50 (4%) |
| Adjusted Rates (b) | 2.4% | 18.1% | 7.1% |
| Terminal Rates (c) | 1/41 (2%) | 1/30 (3%) | 1/22 (5%) |
| Week of First Observation | 104 | 82 | 54 |
| Life Table Tests (d) | P=0.184 | P=0.017 | P=0.331 |
| Incidental Tumor Tests (d) | P=0.457 | P=0.084 | P=0.529 |
| Cochran-Armitage Trend Test (d) | P=0.421 | | |
| Fisher Exact Test (d) | | P=0.030 | P=0.500 |
| **Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma** | | | |
| Overall Rates (a) | 2/50 (4%) | 10/50 (20%) | 2/50 (4%) |
| Adjusted Rates (b) | 4.9% | 26.6% | 7.1% |
| Terminal Rates (c) | 2/41 (5%) | 4/30 (13%) | 1/22 (5%) |
| Week of First Observation | 104 | 82 | 54 |
| Life Table Tests (d) | P=0.239 | P=0.005 | P=0.493 |
| Incidental Tumor Tests (d) | P=0.491 | P=0.026 | P=0.676 |
| Cochran-Armitage Trend Test (d) | P=0.568 | | |
| Fisher Exact Test (d) | | P=0.014 | P=0.691 |
| **Lung: Alveolar/Bronchiolar Adenoma** | | | |
| Overall Rates (a) | 10/50 (20%) | 8/50 (16%) | 4/50 (8%) |
| Adjusted Rates (b) | 23.8% | 23.6% | 17.1% |
| Terminal Rates (c) | 9/41 (22%) | 6/30 (20%) | 3/22 (14%) |
| Week of First Observation | 102 | 78 | 96 |
| Life Table Tests (d) | P=0.367N | P=0.549 | P=0.404N |
| Incidental Tumor Tests (d) | P=0.231N | P=0.478N | P=0.357N |
| Cochran-Armitage Trend Test (d) | P=0.060N | | |
| Fisher Exact Test (d) | | P=0.398N | P=0.074N |
| **Lung: Alveolar/Bronchiolar Carcinoma** | | | |
| Overall Rates (a) | 1/50 (2%) | 3/50 (6%) | 0/50 (0%) |
| Adjusted Rates (b) | 2.4% | 8.7% | 0.0% |
| Terminal Rates (c) | 1/41 (2%) | 1/30 (3%) | 0/22 (0%) |
| Week of First Observation | 104 | 88 | |
| Life Table Tests (d) | P=0.563N | P=0.217 | P=0.624N |
| Incidental Tumor Tests (d) | P=0.401N | P=0.403 | P=0.624N |
| Cochran-Armitage Trend Test (d) | P=0.378N | | |
| Fisher Exact Test (d) | | P=0.309 | P=0.500N |

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Control | 2,500 ppm | 5,000 ppm |
|---|---|---|---|
| **Lung: Alveolar/Bronchiolar Adenoma or Carcinoma** | | | |
| Overall Rates (a) | 11/50 (22%) | 11/50 (22%) | 4/50 (8%) |
| Adjusted Rates (b) | 26.1% | 30.8% | 17.1% |
| Terminal Rates (c) | 10/41 (24%) | 7/30 (23%) | 3/22 (14%) |
| Week of First Observation | 102 | 78 | 96 |
| Life Table Tests (d) | P=0.352N | P=0.311 | P=0.328N |
| Incidental Tumor Tests (d) | P=0.175N | P=0.574 | P=0.286N |
| Cochran-Armitage Trend Test (d) | P=0.043N | | |
| Fisher Exact Test (d) | | P=0.595 | P=0.045N |
| **Hematopoietic System: Malignant Lymphoma, Undifferentiated Type** | | | |
| Overall Rates (a) | 3/50 (6%) | 1/50 (2%) | 1/50 (2%) |
| Adjusted Rates (b) | 7.3% | 3.3% | 4.5% |
| Terminal Rates (c) | 3/41 (7%) | 1/30 (3%) | 1/22 (5%) |
| Week of First Observation | 104 | 104 | 104 |
| Life Table Tests (d) | P=0.392N | P=0.422N | P=0.544N |
| Incidental Tumor Tests (d) | P=0.392N | P=0.422N | P=0.544N |
| Cochran-Armitage Trend Test (d) | P=0.202N | | |
| Fisher Exact Test (d) | | P=0.309N | P=0.309N |
| **Hematopoietic System: Lymphoma, All Malignant** | | | |
| Overall Rates (a) | 4/50 (8%) | 2/50 (4%) | 2/50 (4%) |
| Adjusted Rates (b) | 9.3% | 6.7% | 8.0% |
| Terminal Rates (c) | 3/41 (7%) | 2/30 (7%) | 1/22 (5%) |
| Week of First Observation | 96 | 104 | 92 |
| Life Table Tests (d) | P=0.518N | P=0.485N | P=0.630N |
| Incidental Tumor Tests (d) | P=0.398N | P=0.438N | P=0.434N |
| Cochran-Armitage Trend Test (d) | P=0.252N | | |
| Fisher Exact Test (d) | | P=0.339N | P=0.339N |
| **Circulatory System: Hemangioma** | | | |
| Overall Rates (a) | 3/50 (6%) | 0/50 (0%) | 0/50 (0%) |
| Adjusted Rates (b) | 7.1% | 0.0% | 0.0% |
| Terminal Rates (c) | 2/41 (5%) | 0/30 (0%) | 0/22 (0%) |
| Week of First Observation | 102 | | |
| Life Table Tests (d) | P=0.083N | P=0.180N | P=0.249N |
| Incidental Tumor Tests (d) | P=0.066N | P=0.141N | P=0.217N |
| Cochran-Armitage Trend Test (d) | P=0.037N | | |
| Fisher Exact Test (d) | | P=0.121N | P=0.121N |
| **Circulatory System: Hemangioma or Hemangiosarcoma** | | | |
| Overall Rates (a) | 5/50 (10%) | 1/50 (2%) | 0/50 (0%) |
| Adjusted Rates (b) | 11.5% | 3.3% | 0.0% |
| Terminal Rates (c) | 3/41 (7%) | 1/30 (3%) | 0/22 (0%) |
| Week of First Observation | 97 | 104 | |
| Life Table Tests (d) | P=0.044N | P=0.186N | P=0.117N |
| Incidental Tumor Tests (d) | P=0.029N | P=0.129N | P=0.083N |
| Cochran-Armitage Trend Test (d) | P=0.011N | | |
| Fisher Exact Test (d) | | P=0.102N | P=0.028N |
| **Liver: Hepatocellular Adenoma** | | | |
| Overall Rates (a) | 11/50 (22%) | 9/50 (18%) | 8/49 (16%) |
| Adjusted Rates (b) | 26.0% | 28.8% | 34.7% |
| Terminal Rates (c) | 10/41 (24%) | 8/30 (27%) | 7/22 (32%) |
| Week of First Observation | 96 | 101 | 102 |
| Life Table Tests (d) | P=0.277 | P=0.497 | P=0.320 |
| Incidental Tumor Tests (d) | P=0.314 | P=0.551 | P=0.360 |
| Cochran-Armitage Trend Test (d) | P=0.276N | | |
| Fisher Exact Test (d) | | P=0.402N | P=0.323N |

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Control | 2,500 ppm | 5,000 ppm |
|---|---|---|---|
| **Liver: Hepatocellular Carcinoma** | | | |
| Overall Rates (a) | 5/50 (10%) | 12/50 (24%) | 8/49 (16%) |
| Adjusted Rates (b) | 11.2% | 32.3% | 26.0% |
| Terminal Rates (c) | 3/41 (7%) | 7/30 (23%) | 2/22 (9%) |
| Week of First Observation | 92 | 65 | 43 |
| Life Table Tests (d) | P=0.035 | P=0.019 | P=0.056 |
| Incidental Tumor Tests (d) | P=0.309 | P=0.139 | P=0.463 |
| Cochran-Armitage Trend Test (d) | P=0.237 | | |
| Fisher Exact Test (d) | | P=0.054 | P=0.263 |
| **Liver: Hepatocellular Adenoma or Carcinoma** | | | |
| Overall Rates (a) | 14/50 (28%) | 19/50 (38%) | 15/49 (31%) |
| Adjusted Rates (b) | 31.4% | 51.4% | 50.4% |
| Terminal Rates (c) | 11/41 (27%) | 13/30 (43%) | 8/22 (36%) |
| Week of First Observation | 92 | 65 | 43 |
| Life Table Tests (d) | P=0.023 | P=0.043 | P=0.038 |
| Incidental Tumor Tests (d) | P=0.183 | P=0.211 | P=0.259 |
| Cochran-Armitage Trend Test (d) | P=0.430 | | |
| Fisher Exact Test (d) | | P=0.198 | P=0.474 |
| **Forestomach: Squamous Cell Papilloma** | | | |
| Overall Rates (a) | 2/49 (4%) | 1/50 (2%) | 4/49 (8%) |
| Adjusted Rates (b) | 4.9% | 3.3% | 16.3% |
| Terminal Rates (c) | 2/41 (5%) | 1/30 (3%) | 3/22 (14%) |
| Week of First Observation | 106 | 105 | 79 |
| Life Table Tests (d) | P=0.083 | P=0.609N | P=0.118 |
| Incidental Tumor Tests (d) | P=0.116 | P=0.609N | P=0.201 |
| Cochran-Armitage Trend Test (d) | P=0.238 | | |
| Fisher Exact Test (d) | | P=0.492N | P=0.339 |
| **Harderian Gland: Adenoma** | | | |
| Overall Rates (a) | 3/50 (6%) | 1/50 (2%) | 1/50 (2%) |
| Adjusted Rates (b) | 6.9% | 3.3% | 4.5% |
| Terminal Rates (c) | 2/41 (5%) | 1/30 (3%) | 1/22 (5%) |
| Week of First Observation | 96 | 105 | 104 |
| Life Table Tests (d) | P=0.391N | P=0.419N | P=0.542N |
| Incidental Tumor Tests (d) | P=0.359N | P=0.364N | P=0.499N |
| Cochran-Armitage Trend Test (d) | P=0.202N | | |
| Fisher Exact Test (d) | | P=0.309N | P=0.309N |

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE A4a. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

| Study | Incidence in Controls | | |
|---|---|---|---|
| | Fibroma or Neurofibroma | Sarcoma, Fibrosarcoma, or Neurofibrosarcoma | Fibroma, Neurofibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma |
| **Historical Incidence at EG&G Mason Research Institute** | | | |
| 4, 4'-Methylenedianiline·2HCl | 0/49 | 4/49 | 4/49 |
| Monuron | 0/50 | 2/50 | 2/50 |
| 8-Hydroxyquinoline | 1/50 | 6/50 | 7/50 |
| Butyl benzyl phthalate | 1/50 | 1/50 | 2/50 |
| Di(2-ethylhexyl)phthalate | 2/50 | 0/50 | 2/50 |
| Di(2-ethylhexyl)adipate | 1/50 | 4/50 | 5/50 |
| Guar gum | 0/50 | 6/50 | 6/50 |
| Locust bean gum | 0/50 | 1/50 | 1/50 |
| Gum arabic | 0/49 | 3/49 | 3/49 |
| Tara gum | 0/50 | 0/50 | 0/50 |
| Agar | 1/49 | 0/49 | 1/49 |
| C. I. Basic Red 9 | 0/50 | 0/50 | 0/50 |
| Boric acid | 1/50 | 1/50 | 2/50 |
| 2-Biphenylamine·HCl | 0/50 | 4/50 | 4/50 |
| TOTAL | 7/697 (1.0%) | 32/697 (4.6%) | 39/697 (5.6%) |
| SD (b) | 1.30% | 4.41% | 4.32% |
| Range (c) | | | |
| High | 2/50 | 6/50 | 7/50 |
| Low | 0/50 | 0/50 | 0/50 |
| **Overall Historical Incidence** | | | |
| TOTAL | 36/2,091 (1.7%) | 125/2,091 (6.0%) | 156/2,091 (7.5%) |
| SD (b) | 2.78% | 6.46% | 7.68% |
| Range (c) | | | |
| High | 6/50 | 15/50 | 19/50 |
| Low | 0/50 | 0/50 | 0/50 |

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

| Study | Incidence in Controls | | |
|---|---|---|---|
| | Adenoma | Carcinoma | Adenoma or Carcinoma |
| **Historical Incidence at EG&G Mason Research Institute** | | | |
| 4, 4'-Methylenedianiline·2HCl | 7/49 | 10/49 | 17/49 |
| Monuron | 7/50 | 6/50 | 12/50 |
| 8-Hydroxyquinoline | 9/50 | 5/50 | 14/50 |
| Butyl benzyl phthalate | 4/50 | 9/50 | 13/50 |
| Di(2-ethylhexyl)phthalate | 6/50 | 9/50 | 14/50 |
| Di(2-ethylhexyl)adipate | 6/50 | 7/50 | 13/50 |
| Guar gum | 1/50 | 15/50 | 16/50 |
| Locust bean gum | 6/50 | 15/50 | 18/50 |
| Gum arabic | 4/49 | 13/49 | 16/49 |
| Tara gum | 8/50 | 9/50 | 17/50 |
| Agar | 0/49 | 9/49 | 9/49 |
| C. I. Basic Red 9 | 22/50 | 10/50 | 29/50 |
| Boric acid | 11/50 | 5/50 | 14/50 |
| 2-Biphenylamine·HCl | 5/50 | 9/50 | 14/50 |
| TOTAL | 96/697 (13.8%) | 131/697 (18.8%) | 216/697 (31.0%) |
| SD (b) | 10.46% | 6.45% | 9.09% |
| Range (c) | | | |
| High | 22/50 | 15/50 | 29/50 |
| Low | 0/49 | 5/50 | 9/49 |
| **Overall Historical Incidence** | | | |
| TOTAL | 228/2,084 (10.9%) | 424/2,084 (20.3%) | 627/2,084 (30.1%) |
| SD (b) | 7.29% | 6.85% | 7.78% |
| Range (c) | | | |
| High | (d) 22/50 | 16/50 | (e) 29/50 |
| Low | 0/49 | 4/50 | 8/50 |

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second high: 11/50
(e) Second high: 20/50

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *Skin | (50) | (50) | (50) |
| Epidermal inclusion cyst | | | 2 (4%) |
| Inflammation, acute | 3 (6%) | 2 (4%) | 1 (2%) |
| Inflammation, acute necrotizing | 1 (2%) | 6 (12%) | 1 (2%) |
| *Subcutaneous tissue | (50) | (50) | (50) |
| Mineralization | | 1 (2%) | |
| Abscess, NOS | | 1 (2%) | 1 (2%) |
| Inflammation, active chronic | 1 (2%) | 1 (2%) | |
| Inflammation, chronic | 1 (2%) | | |
| Inflammation, granulomatous | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| *Nasal cavity | (50) | (50) | (50) |
| Inflammation, acute | 2 (4%) | | 2 (4%) |
| *Nasal gland | (50) | (50) | (50) |
| Inflammation, acute | 1 (2%) | | |
| #Lung | (50) | (50) | (50) |
| Aspiration, foreign body | | | 2 (4%) |
| Congestion, NOS | 1 (2%) | | 4 (8%) |
| Hemorrhage | 5 (10%) | 2 (4%) | 1 (2%) |
| Inflammation, acute | 1 (2%) | 1 (2%) | 1 (2%) |
| Inflammation, chronic | 4 (8%) | | 1 (2%) |
| Perivascular cuffing | | | 1 (2%) |
| Hyperplasia, alveolar epithelium | 3 (6%) | 3 (6%) | 2 (4%) |
| Histiocytosis | | 2 (4%) | |
| HEMATOPOIETIC SYSTEM | | | |
| *Multiple organs | (50) | (50) | (50) |
| Depletion, lymphoid | | | 1 (2%) |
| #Bone marrow | (49) | (12) | (48) |
| Hypoplasia, NOS | | | 2 (4%) |
| #Spleen | (48) | (49) | (48) |
| Depletion, lymphoid | 5 (10%) | 11 (22%) | 25 (52%) |
| Hyperplasia, lymphoid | 3 (6%) | 3 (6%) | 1 (2%) |
| Hematopoiesis | 3 (6%) | 11 (22%) | 10 (21%) |
| #Lymph node | (43) | (32) | (42) |
| Pigmentation, NOS | | | 2 (5%) |
| Depletion, lymphoid | | | 1 (2%) |
| #Mandibular lymph node | (43) | (32) | (42) |
| Pigmentation, NOS | | 1 (3%) | |
| Depletion, lymphoid | 1 (2%) | 2 (6%) | 3 (7%) |
| #Cervical lymph node | (43) | (32) | (42) |
| Depletion, lymphoid | | 1 (3%) | |
| #Tracheal lymph node | (43) | (32) | (42) |
| Depletion, lymphoid | | | 1 (2%) |
| #Mediastinal lymph node | (43) | (32) | (42) |
| Depletion, lymphoid | | 1 (3%) | 1 (2%) |
| Hyperplasia, plasma cell | | | 1 (2%) |
| #Pancreatic lymph node | (43) | (32) | (42) |
| Depletion, lymphoid | | | 1 (2%) |
| Angiectasis | 1 (2%) | 1 (3%) | |
| Hyperplasia, lymphoid | 1 (2%) | | |

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| HEMATOPOIETIC SYSTEM (Continued) | | | |
| #Lumbar lymph node | (43) | (32) | (42) |
| Hyperplasia, plasma cell | | 1 (3%) | 1 (2%) |
| #Mesenteric lymph node | (43) | (32) | (42) |
| Hemorrhage | 1 (2%) | 2 (6%) | |
| Inflammation, acute | 1 (2%) | | 1 (2%) |
| Inflammation, active chronic | 1 (2%) | | 1 (2%) |
| Inflammation, granulomatous | | 1 (3%) | |
| Fibrosis | | | 1 (2%) |
| Depletion, lymphoid | | 3 (9%) | 6 (14%) |
| Angiectasis | 10 (23%) | 3 (9%) | 2 (5%) |
| Histiocytosis | | | 2 (5%) |
| Hyperplasia, lymphoid | 3 (7%) | | |
| #Renal lymph node | (43) | (32) | (42) |
| Hyperplasia, NOS | | | 1 (2%) |
| Hyperplasia, plasma cell | | 1 (3%) | |
| #Inguinal lymph node | (43) | (32) | (42) |
| Pigmentation, NOS | 1 (2%) | | |
| Depletion, lymphoid | | 1 (3%) | 1 (2%) |
| Hyperplasia, plasma cell | | 1 (3%) | |
| #Lung | (50) | (50) | (50) |
| Leukemoid reaction | | 1 (2%) | |
| #Liver | (50) | (50) | (49) |
| Hyperplasia, reticulum cell | | | 1 (2%) |
| Hyperplasia, lymphoid | 1 (2%) | | |
| Hematopoiesis | 1 (2%) | 2 (4%) | |
| #Peyer's patch | (50) | (12) | (48) |
| Hyperplasia, lymphoid | 7 (14%) | 1 (8%) | |
| #Thymus | (35) | (7) | (27) |
| Cyst, NOS | 10 (29%) | 2 (29%) | 5 (19%) |
| Hemorrhage | 1 (3%) | | |
| Necrosis, NOS | 1 (3%) | 2 (29%) | 1 (4%) |
| Depletion, lymphoid | 4 (11%) | 5 (71%) | 8 (30%) |
| CIRCULATORY SYSTEM | | | |
| #Mesenteric lymph node | (43) | (32) | (42) |
| Thrombus, organized | 1 (2%) | 1 (3%) | |
| #Lung | (50) | (50) | (50) |
| Perivasculitis | 1 (2%) | 2 (4%) | |
| #Heart | (50) | (12) | (50) |
| Mineralization | | 1 (8%) | 2 (4%) |
| Inflammation, chronic | 1 (2%) | | |
| Degeneration, NOS | 2 (4%) | | |
| *Pulmonary artery | (50) | (50) | (50) |
| Hyperplasia, NOS | 1 (2%) | | |
| *Cystic artery | (50) | (50) | (50) |
| Necrosis, fibrinoid | | | 1 (2%) |
| *Sup. pancreaticoduodenal artery | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | |
| *Mesenteric artery | (50) | (50) | (50) |
| Thrombus, organized | 1 (2%) | | |
| #Liver | (50) | (50) | (49) |
| Thrombosis, NOS | 1 (2%) | | |
| #Forestomach | (49) | (50) | (49) |
| Lymphangiectasis | | 1 (2%) | |
| #Testis | (49) | (50) | (47) |
| Perivasculitis | | | 1 (2%) |

**TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)**

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| DIGESTIVE SYSTEM | | | |
| *Hard palate | (50) | (50) | (50) |
| Inflammation, acute | 1 (2%) | | |
| Granuloma, foreign body | 1 (2%) | | |
| *Tooth | (50) | (50) | (50) |
| Abscess, NOS | 1 (2%) | | |
| Inflammation, chronic | 1 (2%) | | |
| #Salivary gland | (49) | (49) | (47) |
| Inflammation, chronic | 36 (73%) | 33 (67%) | 13 (28%) |
| Atrophy, NOS | 1 (2%) | | |
| #Liver | (50) | (50) | (49) |
| Rupture | 1 (2%) | | |
| Inflammation, acute | 1 (2%) | 2 (4%) | |
| Inflammation, chronic | 3 (6%) | 9 (18%) | 1 (2%) |
| Necrosis, coagulative | 3 (6%) | 8 (16%) | 7 (14%) |
| Nuclear enlargement | | 1 (2%) | |
| Cytoplasmic vacuolization | 2 (4%) | 3 (6%) | 1 (2%) |
| Basophilic cyto change | | 2 (4%) | 3 (6%) |
| Clear cell change | 2 (4%) | 1 (2%) | |
| Hepatocytomegaly | | 1 (2%) | |
| Atrophy, NOS | | 1 (2%) | |
| Angiectasis | 1 (2%) | | |
| #Liver/periportal | (50) | (50) | (49) |
| Inflammation, chronic | | 1 (2%) | |
| #Liver/Kupffer cell | (50) | (50) | (49) |
| Hyperplasia, NOS | | 1 (2%) | |
| *Gallbladder | (50) | (50) | (50) |
| Inflammation, chronic | | 2 (4%) | |
| #Bile duct | (50) | (50) | (49) |
| Dilatation, NOS | | 1 (2%) | |
| Hyperplasia, NOS | | 1 (2%) | |
| #Pancreas | (49) | (48) | (45) |
| Dilatation/ducts | 1 (2%) | | |
| Inflammation, acute | | 1 (2%) | 1 (2%) |
| Inflammation, chronic | 29 (59%) | 28 (58%) | 21 (47%) |
| Fibrosis | | | 1 (2%) |
| Cytoplasmic change, NOS | 3 (6%) | | 1 (2%) |
| Atrophy, NOS | 3 (6%) | 1 (2%) | 2 (4%) |
| Hyperplasia, NOS | 3 (6%) | 1 (2%) | |
| #Pancreatic duct | (49) | (48) | (45) |
| Hyperplasia, NOS | 1 (2%) | 1 (2%) | |
| #Stomach | (49) | (50) | (49) |
| Cyst, NOS | 1 (2%) | 1 (2%) | |
| Epidermal inclusion cyst | | 1 (2%) | |
| #Glandular stomach | (49) | (50) | (49) |
| Mineralization | | 1 (2%) | |
| Inflammation, acute | | 1 (2%) | 1 (2%) |
| Inflammation, chronic | 7 (14%) | 8 (16%) | 2 (4%) |
| Hyperplasia, epithelial | 2 (4%) | 1 (2%) | |
| #Forestomach | (49) | (50) | (49) |
| Inflammation, chronic | | 4 (8%) | |
| Necrosis, NOS | | 1 (2%) | |
| Hyperplasia, epithelial | 1 (2%) | | 3 (6%) |
| Hyperkeratosis | | 2 (4%) | 1 (2%) |
| Metaplasia, squamous | | 1 (2%) | |
| #Peyer's patch | (50) | (12) | (48) |
| Hyperplasia, NOS | 1 (2%) | | |
| #Duodenum | (50) | (12) | (48) |
| Congestion, NOS | | 1 (8%) | |

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| DIGESTIVE SYSTEM (Continued) | | | |
| #Jejunum | (50) | (12) | (48) |
| Ulcer, acute | 1 (2%) | | |
| Necrosis, coagulative | 1 (2%) | | |
| Hyperplasia, epithelial | | | 1 (2%) |
| #Colon | (49) | (12) | (46) |
| Inflammation, NOS | | | 1 (2%) |
| URINARY SYSTEM | | | |
| #Kidney | (50) | (50) | (50) |
| Hydronephrosis | 2 (4%) | | 3 (6%) |
| Cyst, NOS | | | 1 (2%) |
| Glomerulonephritis, NOS | 5 (10%) | 3 (6%) | 1 (2%) |
| Pyelonephritis, NOS | 1 (2%) | 3 (6%) | 3 (6%) |
| Inflammation, acute | | 1 (2%) | 1 (2%) |
| Inflammation, chronic | 47 (94%) | 37 (74%) | 34 (68%) |
| Fibrosis | | | 1 (2%) |
| Glomerulosclerosis, NOS | 1 (2%) | 6 (12%) | 2 (4%) |
| Infarct, NOS | | 1 (2%) | |
| Metaplasia, osseous | 3 (6%) | 2 (4%) | |
| #Renal papilla | (50) | (50) | (50) |
| Necrosis, coagulative | | 1 (2%) | 1 (2%) |
| #Kidney/glomerulus | (50) | (50) | (50) |
| Adhesion, NOS | | | 1 (2%) |
| #Kidney/tubule | (50) | (50) | (50) |
| Mineralization | 24 (48%) | 21 (42%) | 14 (28%) |
| Cast, NOS | | 1 (2%) | |
| Degeneration, NOS | | 1 (2%) | |
| Necrosis, NOS | | 1 (2%) | 1 (2%) |
| Pigmentation, NOS | | 1 (2%) | |
| Atrophy, NOS | 2 (4%) | 2 (4%) | 5 (10%) |
| Hyperplasia, epithelial | 1 (2%) | | |
| Regeneration, NOS | 31 (62%) | 22 (44%) | 15 (30%) |
| #Kidney/pelvis | (50) | (50) | (50) |
| Hemorrhage | | 1 (2%) | |
| *Ureter | (50) | (50) | (50) |
| Inflammation, acute | | | 1 (2%) |
| Hyperplasia, epithelial | | | 1 (2%) |
| #Urinary bladder | (50) | (19) | (49) |
| Calculus, gross observation only | 2 (4%) | 4 (21%) | |
| Calculus, microscopic examination | | 1 (5%) | |
| Hemorrhage | | | 1 (2%) |
| Inflammation, acute | | 1 (5%) | |
| Inflammation, chronic | 12 (24%) | 9 (47%) | 12 (24%) |
| Fibrosis | | 1 (5%) | |
| Hyperplasia, epithelial | | 2 (11%) | |
| Angiectasis | | | 1 (2%) |
| *Urethra | (50) | (50) | (50) |
| Calculus, gross observation only | 1 (2%) | | |
| Calculus, microscopic examination | 13 (26%) | | 7 (14%) |
| Inflammation, acute | | | 1 (2%) |
| Inflammation, chronic | | 1 (2%) | |
| *Urethral gland | (50) | (50) | (50) |
| Inflammation, acute | | 1 (2%) | |

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| ENDOCRINE SYSTEM | | | |
| #Anterior pituitary | (35) | (9) | (47) |
| Cyst, NOS | 3 (9%) | | 3 (6%) |
| Hyperplasia, NOS | 4 (11%) | | 5 (11%) |
| #Pituitary posterior | (35) | (9) | (47) |
| Cyst, NOS | 1 (3%) | | |
| #Adrenal cortex | (50) | (11) | (48) |
| Hyperplasia, NOS | 1 (2%) | 1 (9%) | 2 (4%) |
| #Thyroid | (44) | (12) | (48) |
| Cyst, NOS | | | 1 (2%) |
| Follicular cyst, NOS | 2 (5%) | | |
| Inflammation, NOS | | 1 (8%) | |
| Hyperplasia, follicular cell | 1 (2%) | | 2 (4%) |
| #Pancreatic islets | (49) | (48) | (45) |
| Hyperplasia, NOS | 7 (14%) | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| *Mammary gland | (50) | (50) | (50) |
| Dilatation/ducts | 1 (2%) | | 1 (2%) |
| *Epididymal lumen | (50) | (50) | (50) |
| Mineralization | | 1 (2%) | |
| Dilatation, NOS | | 1 (2%) | |
| *Penis | (50) | (50) | (50) |
| Inflammation, acute | 1 (2%) | 1 (2%) | |
| Inflammation, acute necrotizing | | | 1 (2%) |
| *Prepuce | (50) | (50) | (50) |
| Inflammation, acute necrotizing | | 2 (4%) | 3 (6%) |
| Inflammation, active chronic | | 1 (2%) | |
| Acanthosis | | | 1 (2%) |
| *Preputial gland | (50) | (50) | (50) |
| Dilatation/ducts | 3 (6%) | 1 (2%) | 2 (4%) |
| Abscess, NOS | | 1 (2%) | 2 (4%) |
| Inflammation, active chronic | 2 (4%) | 4 (8%) | 1 (2%) |
| Inflammation, chronic | | 4 (8%) | |
| Atrophy, NOS | | | 1 (2%) |
| Hyperplasia, NOS | | | 1 (2%) |
| Hyperkeratosis | 2 (4%) | | |
| #Prostate | (48) | (9) | (46) |
| Inflammation, acute | | 1 (11%) | 1 (2%) |
| Inflammation, chronic | 5 (10%) | 2 (22%) | 3 (7%) |
| *Seminal vesicle | (50) | (50) | (50) |
| Distention | 2 (4%) | | 3 (6%) |
| Inflammation, acute | | 1 (2%) | 1 (2%) |
| Inflammation, active chronic | | 1 (2%) | 3 (6%) |
| Inflammation, chronic | | | 1 (2%) |
| Fibrosis | | | 1 (2%) |
| #Periprostatic tissue | (48) | (9) | (46) |
| Inflammation, chronic | 1 (2%) | | |
| *Coagulating gland | (50) | (50) | (50) |
| Distention | | | 1 (2%) |
| #Testis | (49) | (50) | (47) |
| Mineralization | | 3 (6%) | 1 (2%) |
| Cyst, NOS | | | 1 (2%) |
| Inflammation, acute | | | 1 (2%) |
| Atrophy, NOS | 3 (6%) | 6 (12%) | 27 (57%) |
| Hyperplasia, interstitial cell | | | 7 (15%) |
| Histiocytosis | | 1 (2%) | |

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| REPRODUCTIVE SYSTEM (Continued) | | | |
| *Epididymis | (50) | (50) | (50) |
| Mineralization | | | 1 (2%) |
| Inflammation, active chronic | | 1 (2%) | |
| Inflammation, chronic | | 2 (4%) | |
| Granuloma, spermatic | | 1 (2%) | |
| *Vas deferens | (50) | (50) | (50) |
| Inflammation, chronic | | 1 (2%) | |
| NERVOUS SYSTEM | | | |
| #Cerebrum | (50) | (50) | (50) |
| Inflammation, acute | | | 1 (2%) |
| Necrosis, NOS | | | 1 (2%) |
| #Brain/thalamus | (50) | (50) | (50) |
| Mineralization | 39 (78%) | 34 (68%) | 22 (44%) |
| SPECIAL SENSE ORGANS | | | |
| *Cornea, external epithelium | (50) | (50) | (50) |
| Ulcer, NOS | 1 (2%) | | |
| *Cornea, substantia propria | (50) | (50) | (50) |
| Inflammation, acute necrotizing | 1 (2%) | | |
| Inflammation, active chronic | | 1 (2%) | |
| Fibrosis | 1 (2%) | 1 (2%) | |
| *Eye/iris | (50) | (50) | (50) |
| Synechia, anterior | | 1 (2%) | 1 (2%) |
| Synechia, posterior | | | 1 (2%) |
| *Nasolacrimal duct | (50) | (50) | (50) |
| Inflammation, NOS | 3 (6%) | 2 (4%) | 3 (6%) |
| *Harderian gland | (50) | (50) | (50) |
| Inflammation, chronic focal | | 2 (4%) | |
| Hyperplasia, NOS | 2 (4%) | | |
| MUSCULOSKELETAL SYSTEM | | | |
| *Tarsal joint | (50) | (50) | (50) |
| Ankylosis | 5 (10%) | 8 (16%) | 1 (2%) |
| Osteoarthritis | 5 (10%) | 8 (16%) | |
| *Abdominal muscle | (50) | (50) | (50) |
| Inflammation, chronic | | | 1 (2%) |
| BODY CAVITIES | | | |
| *Abdominal cavity | (50) | (50) | (50) |
| Cyst, NOS | | 1 (2%) | |
| Hemoperitoneum | 2 (4%) | 3 (6%) | |
| *Peritoneum | (50) | (50) | (50) |
| Inflammation, acute | | | 1 (2%) |

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| ALL OTHER SYSTEMS | | | |
| *Multiple organs | (50) | (50) | (50) |
| Inflammation, NOS | | 2 (4%) | 1 (2%) |
| Inflammation, granulomatous | 1 (2%) | | |
| Bacterial septicemia | | | 1 (2%) |
| Omentum | | | |
| Mineralization | 1 | | 1 |
| Inflammation, active chronic | 1 | | |
| Fibrosis | 1 | 1 | 1 |
| Necrosis, NOS | | 1 | 1 |
| Jejunal mesentery | | | |
| Cyst, NOS | | | 1 |
| Inflammation, active chronic | | | 1 |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| None | | | |

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

# APPENDIX B

# SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID

**TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID**

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *Skin | (50) | (50) | (50) |
| Squamous cell carcinoma | | | 1 (2%) |
| *Subcutaneous tissue | (50) | (50) | (50) |
| Sarcoma, NOS | 1 (2%) | 1 (2%) | |
| Fibrosarcoma | 1 (2%) | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #Lung | (50) | (50) | (50) |
| Hepatocellular carcinoma, metastatic | 1 (2%) | 1 (2%) | 1 (2%) |
| Alveolar/bronchiolar adenoma | 1 (2%) | 4 (8%) | 4 (8%) |
| Alveolar/bronchiolar carcinoma | | 1 (2%) | |
| Osteosarcoma, metastatic | | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | |
| *Multiple organs | (50) | (50) | (50) |
| Malignant lymphoma, NOS | 2 (4%) | | 1 (2%) |
| Malignant lymphoma, undiffer type | 6 (12%) | 3 (6%) | 5 (10%) |
| Malignant lymphoma, lymphocytic type | 2 (4%) | | |
| Malignant lymphoma, histiocytic type | | 1 (2%) | |
| Malignant lymphoma, mixed type | 1 (2%) | 5 (10%) | 4 (8%) |
| #Spleen | (49) | (34) | (50) |
| Squamous cell carcinoma, metastatic | | | 1 (2%) |
| Malignant lymphoma, undiffer type | 1 (2%) | | 1 (2%) |
| #Pancreatic lymph node | (47) | (22) | (46) |
| Sarcoma, NOS, metastatic | | 1 (5%) | |
| #Thymus | (38) | (6) | (36) |
| Malignant lymphoma, lymphocytic type | 1 (3%) | | |
| CIRCULATORY SYSTEM | | | |
| *Multiple organs | (50) | (50) | (50) |
| Hemangiosarcoma | | 1 (2%) | |
| Hemangiosarcoma, unclear primary or metastatic | | 1 (2%) | |
| #Spleen | (49) | (34) | (50) |
| Hemangiosarcoma | 1 (2%) | | |
| #Omentum | (50) | (16) | (50) |
| Hemangiosarcoma | | 1 (6%) | |
| #Uterus | (50) | (31) | (49) |
| Hemangioma | | | 1 (2%) |
| Hemangiopericytoma, NOS | | | 1 (2%) |
| #Uterus/endometrium | (50) | (31) | (49) |
| Hemangioma | 1 (2%) | | |
| #Ovary/parovarian | (49) | (50) | (45) |
| Hemangioma | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | |
| #Liver | (50) | (50) | (50) |
| Squamous cell carcinoma, metastatic | | | 1 (2%) |
| Hepatocellular adenoma | 2 (4%) | 2 (4%) | 3 (6%) |
| Hepatocellular carcinoma | 3 (6%) | 2 (4%) | 3 (6%) |

**TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)**

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| DIGESTIVE SYSTEM (Continued) | | | |
| #Pancreas | (50) | (11) | (50) |
| Squamous cell carcinoma, metastatic | | | 1 (2%) |
| #Forestomach | (50) | (16) | (50) |
| Squamous cell papilloma | 1 (2%) | 2 (13%) | |
| Squamous cell carcinoma | | | 1 (2%) |
| URINARY SYSTEM | | | |
| None | | | |
| ENDOCRINE SYSTEM | | | |
| #Anterior pituitary | (39) | (10) | (43) |
| Adenoma, NOS | 3 (8%) | 3 (30%) | 2 (5%) |
| #Pancreatic islets | (50) | (11) | (50) |
| Islet cell adenoma | | 1 (9%) | |
| REPRODUCTIVE SYSTEM | | | |
| *Mammary gland | (50) | (50) | (50) |
| Adenocarcinoma, NOS | 1 (2%) | 1 (2%) | 1 (2%) |
| #Uterus | (50) | (31) | (49) |
| Endometrial stromal polyp | | | 3 (6%) |
| Endometrial stromal sarcoma | | 1 (3%) | 1 (2%) |
| #Uterus/myometrium | (50) | (31) | (49) |
| Leiomyoma | | 1 (3%) | |
| NERVOUS SYSTEM | | | |
| None | | | |
| SPECIAL SENSE ORGANS | | | |
| *Eye | (50) | (50) | (50) |
| Carcinoma, NOS, invasive | | 1 (2%) | |
| *Harderian gland | (50) | (50) | (50) |
| Carcinoma, NOS | | 1 (2%) | |
| Adenoma, NOS | | | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | |
| *Bone | (50) | (50) | (50) |
| Osteoma | | | 1 (2%) |
| *Vertebral column | (50) | (50) | (50) |
| Osteosarcoma | | 1 (2%) | |
| BODY CAVITIES | | | |
| None | | | |
| ALL OTHER SYSTEMS | | | |
| None | | | |

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| Animals initially in study | 50 | 50 | 50 |
| Natural death | 9 | 9 | 7 |
| Moribund sacrifice | 9 | 6 | 5 |
| Terminal sacrifice | 32 | 33 | 37 |
| Accidentally killed, nda | | 2 | 1 |
| TUMOR SUMMARY | | | |
| Total animals with primary tumors** | 25 | 27 | 26 |
| Total primary tumors | 28 | 34 | 35 |
| Total animals with benign tumors | 8 | 11 | 14 |
| Total benign tumors | 8 | 13 | 16 |
| Total animals with malignant tumors | 20 | 15 | 17 |
| Total malignant tumors | 20 | 20 | 18 |
| Total animals with secondary tumors## | 1 | 4 | 2 |
| Total secondary tumors | 1 | 4 | 4 |
| Total animals with tumors uncertain--benign or malignant | | | 1 |
| Total uncertain tumors | | | 1 |
| Total animals with tumors uncertain--primary or metastatic | | 1 | |
| Total uncertain tumors | | 1 | |

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
## Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

## TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID: UNTREATED CONTROL

| ANIMAL NUMBER | 02828 | 02827 | 02826 | 02829 | 02822 | 00101 | 01111 | 03038 | 00202 | 01919 | 01515 | 03737 | 03232 | 03535 | 04444 | 04949 | 00606 | 00303 | 00404 | 00505 | 00707 | 00808 | 00909 | 01010 | 01212 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 05303 | 07101 | 08000 | 08202 | 09101 | 09202 | 09404 | 09404 | 09707 | 09707 | 09808 | 09908 | 10101 | 10202 | 10202 | 10204 | 10606 | 10606 | 10606 | 10606 | 10606 | 10606 | 10606 | 10606 | 10606 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | + | + | + | + | + | + | + | + | + | N | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibrosarcoma | X | | | | | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Trachea | + | + | + | − | + | − | − | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + |
| Thymus | − | − | − | + | − | − | + | − | − | + | − | − | − | + | + | − | + | + | + | + | + | + | + | + | + |
| Malignant lymphoma, lymphocytic type | | | | | | | | | | | | | | X | | | | | | | | | | | |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | − | + | − | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Hepatocellular carcinoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | + | + | + | + | N | + | + | N | N | + | + | + | + | N | + | + | + | + | N | + | + | + | + | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Esophagus | + | + | − | + | − | − | + | + | + | − | + | + | − | + | + | + | + | − | + | + | + | + | + | + | + |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Small intestine | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | − | + | + | − | + | + | + | − | + | + | − | + | − | − | + | + | − | + | − | − | + | + | + | + | + |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Adrenal | + | − | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid | + | + | + | − | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid | + | + | + | − | + | − | − | + | + | + | − | + | + | + | − | − | − | − | + | − | − | + | − | + | − |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | N | N | N | + | N | + | N | N | N | N | N | N | N | + | N | N | + | N | N | + | N | N | N | N |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Malignant lymphoma, NOS | | | | | | | | | | | X | | X | | | | | | | | | | | | |
| Malignant lymphoma, undiffer type | | | | | X | X | | X | | | | | | | | X | X | | | | | | | | |
| Malignant lymphoma, lymphocytic type | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Malignant lymphoma, mixed type | | | | | | | | | | | | | | | | | | | | | | | | | |

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

## TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

| ANIMAL NUMBER | 0013 | 0014 | 0016 | 0017 | 0018 | 0020 | 0021 | 0023 | 0024 | 0025 | 0030 | 0031 | 0033 | 0034 | 0036 | 0039 | 0040 | 0041 | 0042 | 0043 | 0045 | 0046 | 0047 | 0048 | 0050 | TOTAL: |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | *50 | |
| Sarcoma, NOS | | | | | | | | | | | | | | | | X | | | | | | | | | 1 | |
| Fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Hepatocellular carcinoma, metastatic | | | | | | | | | | | | | | | X | | | | | | | | | | 1 | |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | 1 | |
| Trachea | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | 44 | |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Hemangiosarcoma | | | | | | | | | | | | X | | | | | | | | | | | | | 1 | |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Lymph nodes | + | + | + | – | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 | |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | 38 | |
| Malignant lymphoma, lymphocytic type | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Hepatocellular adenoma | | | | | X | | | | | | | | | | | | | | | | | | | | 2 | |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | X | | | X | | | | | | | 3 | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Gallbladder & common bile duct | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | *50 | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Esophagus | + | + | + | + | + | – | – | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | 41 | |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | 39 | |
| Adenoma, NOS | | X | | | | | | | | | | | | | | | | | | | | | X | | 3 | |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Thyroid | + | + | + | + | – | + | – | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | 45 | |
| Parathyroid | + | + | + | + | – | – | – | – | + | – | + | + | + | – | + | + | – | – | + | – | – | + | + | + | 28 | |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | N | + | N | + | N | N | N | N | N | N | N | + | + | N | N | N | N | N | N | + | N | N | N | *50 | |
| Adenocarcinoma, NOS | | | | | | | | | | | | | X | | | | | | | | | | | | 1 | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Hemangioma | | | | | | | X | | | | | | | | | | | | | | | | | | 1 | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | 49 | |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 | |
| Malignant lymphoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | X | | | | | 6 | |
| Malignant lymphoma, lymphocytic type | | | | | | | | | | | | | | | | | | | | | | X | | | 2 | |
| Malignant lymphoma, mixed type | | | | | | | X | | | | | | | | | | | | | | | | | | 1 | |

* Animals necropsied

## TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID: LOW DOSE

| ANIMAL NUMBER | 0 3 2 | 0 3 3 | 0 4 1 | 0 2 8 | 0 0 2 | 0 2 3 | 0 1 0 | 0 2 7 | 0 1 6 | 0 0 4 | 0 0 5 | 0 1 7 | 0 1 8 | 0 0 3 | 0 4 8 | 0 1 3 | 0 5 0 | 0 0 1 | 0 0 6 | 0 0 7 | 0 0 8 | 0 0 9 | 0 1 1 | 0 1 2 | 0 1 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 0 1 3 | 0 1 3 | 0 6 8 | 0 7 0 | 0 7 3 | 0 7 4 | 0 7 7 | 0 8 4 | 0 9 1 | 0 9 5 | 0 9 8 | 0 9 7 | 0 9 7 | 0 9 9 | 0 9 9 | 1 0 2 | 1 0 3 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | N | + | + | + | + | + | + | N | + | N | N | + | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Sarcoma, NOS | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma, metastatic | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Osteosarcoma, metastatic | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Spleen | + | − | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | − | − | + | + | + |
| Lymph nodes | + | − | + | + | + | + | + | + | − | − | + | + | + | + | + | − | + | − | − | + | − | − | − | + | − |
| Sarcoma, NOS, metastatic | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Thymus | + | − | + | − | − | + | + | − | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | − | + | + | + | + | + | − | − | − | − | − | + | − | − | − | − | − | − | − | − | − | − |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | X | | | | | | | | | | | | | | X | | | | | | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | + | + | + | + | N | + | N | + | + | + | N | + | + | + | + | + | + | + | N | + | + | + | + | + |
| Pancreas | + | + | + | + | − | + | + | + | + | − | − | − | − | − | + | − | − | − | − | − | − | − | − | − | − |
| Esophagus | + | + | + | − | + | − | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | + | − |
| Stomach | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | + | + | − | − | − | − | − | − | − |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Small intestine | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − | + | − | − |
| Large intestine | + | + | + | + | + | + | + | − | + | − | − | − | + | − | − | − | − | − | − | − | − | − | − | − | − |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | − | − | − | + | − | − | + | − | − | − | − | − | − | − | − |
| Urinary bladder | + | + | + | + | − | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | − | − | − | − | − | − | + | − | − | − | − | − | − | − | − | − | − |
| Adenoma, NOS | | | | X | | | | | | | | | | | X | | | | | | | | | | |
| Adrenal | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Thyroid | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Parathyroid | + | − | − | − | + | + | + | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Pancreatic islets | + | + | + | + | − | + | + | + | + | − | − | − | − | − | + | − | − | − | − | − | − | − | − | − | − |
| Islet cell adenoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | − | + | − | − | + | − | + | + | − | − | + | + | + | − | + | − |
| Leiomyoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Endometrial stromal sarcoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N |
| Carcinoma, NOS, invasive | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Harderian gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Carcinoma, NOS | | | | | | | | | | | | | | | | X | | | | | | | | | |
| **MUSCULOSKELETAL SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Osteosarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma, unclear primary or metastatic | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | X | | | | | | | | | | | | X | |
| Malignant lymphoma, histiocytic type | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Malignant lymphoma, mixed type | | | | | | | | | | X | | | X | | | | | | X | | | | | | |

## TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

| ANIMAL NUMBER | 0 1 5 | 0 1 9 | 0 2 0 | 0 2 1 | 0 2 2 | 0 2 4 | 0 2 5 | 0 2 6 | 0 2 9 | 0 3 0 | 0 3 1 | 0 3 4 | 0 3 5 | 0 3 6 | 0 3 7 | 0 3 8 | 0 3 9 | 0 4 0 | 0 4 2 | 0 4 3 | 0 4 4 | 0 4 5 | 0 4 6 | 0 4 7 | 0 4 9 | TOTAL TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | + | N | N | *50 |
| Sarcoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular carcinoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Alveolar/bronchiolar adenoma | | | X | X | | | | | | | | | | X | | | | | | | | | | | | 4 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Osteosarcoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Trachea | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 7 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | – | – | – | | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 9 |
| Spleen | + | + | – | + | – | + | – | – | – | – | + | – | + | – | + | + | – | – | – | + | + | + | + | + | – | 34 |
| Lymph nodes | – | – | – | + | – | + | + | – | – | – | + | – | + | – | – | – | – | – | – | + | – | – | – | + | – | 22 |
| Sarcoma, NOS, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | – | – | – | – | | – | – | – | – | – | – | | + | – | – | – | – | – | – | | – | – | – | – | – | 6 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | – | – | | | | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 9 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | – | – | – | – | | – | – | – | – | | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 9 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | X | | | | | | | | | | | | | | | | | | | | | | | | X | 2 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | + | N | + | + | + | N | + | + | + | + | + | + | + | + | + | + | *50 |
| Pancreas | – | – | – | – | – | – | – | + | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | + | – | 11 |
| Esophagus | + | – | – | – | – | – | – | + | – | – | – | – | – | | – | – | – | – | - | – | – | – | – | – | – | 10 |
| Stomach | – | – | – | – | + | – | + | – | – | – | – | – | – | – | – | – | + | + | + | – | – | – | – | – | – | 16 |
| Squamous cell papilloma | | | | | X | | | | | | | | | | | | X | | | | | | | | | 2 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| Small intestine | – | + | – | – | – | – | | – | – | – | – | – | + | – | – | – | – | – | – | – | – | – | – | – | – | 12 |
| Large intestine | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 9 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | – | – | – | – | + | – | – | – | – | – | + | – | + | – | – | – | – | – | – | + | – | – | + | – | – | 17 |
| Urinary bladder | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 8 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | – | – | – | – | + | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 10 |
| Adenoma, NOS | | | | | X | | | | | | | | | | | | | | | | | | | | | 3 |
| Adrenal | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 9 |
| Thyroid | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 8 |
| Parathyroid | – | – | – | – | – | – | – | – | | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 5 |
| Pancreatic islets | | – | – | – | – | – | – | + | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | + | – | 11 |
| Islet cell adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | *50 |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | – | – | – | – | + | – | + | – | – | – | – | + | + | – | – | + | + | 31 |
| Leiomyoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Endometrial stromal sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Carcinoma, NOS, invasive | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Harderian gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Carcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **MUSCULOSKELETAL SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Osteosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Hemangiosarcoma, unclear prim or met | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Malignant lymphoma, undiffer type | | | | | | | | | | | X | | | | | | | | | | | | | | | 3 |
| Malignant lymphoma, histiocytic type | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Malignant lymphoma, mixed type | | | | | | | | | | | | | | | | | | | | X | | | | X | | 5 |

* Animals necropsied

**TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID: HIGH DOSE**

| ANIMAL NUMBER | 0121 | 0241 | 0371 | 0311 | 0321 | 0211 | 0071 | 0341 | 0481 | 0451 | 0501 | 0331 | 0471 | 0011 | 0021 | 0031 | 0041 | 0051 | 0061 | 0081 | 0091 | 0101 | 0111 | 0131 | 0141 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 0001 | 0721 | 0886 | 0899 | 0900 | 0933 | 0955 | 0977 | 0977 | 0999 | 1011 | 1022 | 1022 | 1055 | 1055 | 1055 | 1055 | 1055 | 1055 | 1055 | 1055 | 1055 | 1055 | 1055 | 1055 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | N | + | + | N | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma, metastatic | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma | | | | | | | | | | X | | | | | | | | | | | | X | X | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma, metastatic | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Lymph nodes | – | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | – | + | + | + | + | + | – | + |
| Thymus | + | – | – | – | + | – | – | + | – | – | – | + | – | – | – | + | + | + | + | + | + | + | + | – | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | – | + | + | – | – | + | + | – | + | + | + | + | + | + | + | + | – | – | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma, metastatic | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Hepatocellular carcinoma | | | | | | | | X | | | | | | | X | | | | | | | X | | | |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | + | + | + | + | N | + | + | N | + | + | + | + | + | + | + | N | + | N |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma, metastatic | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | – | + | + | + | – | + | – | + | + | + | + | + | + | – | + | – | + | + | – | + |
| Adenoma, NOS | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Adrenal | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | – | + | + |
| Parathyroid | – | + | – | + | – | + | + | – | – | – | – | – | + | – | – | + | + | + | + | + | – | – | – | + | + |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | N | N | + | N | N | + | N | + | N | + | N | + | N | N | + | + | + | + | N | N | N | + | + |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Uterus | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endometrial stromal polyp | | | | | | | | | | X | X | | | | | | | | | | | | | | X |
| Endometrial stromal sarcoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiopericytoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | – | + | + | + | + | + | + | – |
| Hemangioma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | X | | | | | |
| **MUSCULOSKELETAL SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Osteoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Malignant lymphoma, NOS | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | X | | X | | | | | | | | | |
| Malignant lymphoma, mixed type | | | | | | | X | | | | | X | X | | | | | | | | | | | | |

**TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)**

| ANIMAL NUMBER | 015 | 016 | 017 | 018 | 019 | 020 | 022 | 023 | 025 | 026 | 027 | 028 | 029 | 030 | 035 | 036 | 038 | 039 | 040 | 041 | 042 | 043 | 044 | 046 | 049 | TOTAL: |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | *50 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lungs and bronchi | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular carcinoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Alveolar/bronchiolar adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Trachea | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell carcinoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Malignant lymphoma, undiffer type | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph nodes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| Thymus | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | 36 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | 43 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell carcinoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular adenoma | | | | | | | | X | | | | | | | X | | | | | | | | | | | 3 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Bile duct | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder & common bile duct | + | + | + | + | + | + | + | N | + | + | N | + | N | + | + | N | N | N | N | + | + | + | + | + | + | *50 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell carcinoma, metastatic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Esophagus | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | 46 |
| Stomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Small intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Large intestine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | 43 |
| Adenoma, NOS | | | | | | X | | | | | | | | | | | | | | | | | | | | 2 |
| Adrenal | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | 48 |
| Thyroid | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Parathyroid | + | – | + | – | + | – | + | + | – | + | + | – | + | + | + | – | + | + | – | – | – | + | – | – | + | 28 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | N | + | + | N | N | N | + | N | N | N | + | N | N | + | N | N | N | + | N | N | N | N | N | N | N | *50 |
| Adenocarcinoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Endometrial stromal polyp | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Endometrial stromal sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangioma | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| Hemangiopericytoma, NOS | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| Ovary | – | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | 45 |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Adenoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **MUSCULOSKELETAL SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Osteoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs, NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | *50 |
| Malignant lymphoma, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Malignant lymphoma, undiffer type | | | X | X | | | | | | | | | | | | | | | | X | | | | | | 5 |
| Malignant lymphoma, mixed type | | | | | | | | | | | | | | | X | | | | | | | | | | | 4 |

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID

| | Control | 2,500 ppm | 5,000 ppm |
|---|---|---|---|
| **Lung: Alveolar/Bronchiolar Adenoma** | | | |
| Overall Rates (a) | 1/50 (2%) | 4/50 (8%) | 4/50 (8%) |
| Adjusted Rates (b) | 3.0% | 12.1% | 10.3% |
| Terminal Rates (c) | 1/33 (3%) | 4/33 (12%) | 3/37 (8%) |
| Week of First Observation | 105 | 105 | 99 |
| Life Table Tests (d) | P=0.183 | P=0.178 | P=0.215 |
| Incidental Tumor Tests (d) | P=0.169 | P=0.178 | P=0.189 |
| Cochran-Armitage Trend Test (d) | P=0.146 | | |
| Fisher Exact Test (d) | | P=0.181 | P=0.181 |
| **Lung: Alveolar/Bronchiolar Adenoma or Carcinoma** | | | |
| Overall Rates (a) | 1/50 (2%) | 5/50 (10%) | 4/50 (8%) |
| Adjusted Rates (b) | 3.0% | 14.4% | 10.3% |
| Terminal Rates (c) | 1/33 (3%) | 4/33 (12%) | 3/37 (8%) |
| Week of First Observation | 105 | 97 | 99 |
| Life Table Tests (d) | P=0.197 | P=0.101 | P=0.215 |
| Incidental Tumor Tests (d) | P=0.170 | P=0.092 | P=0.189 |
| Cochran-Armitage Trend Test (d) | P=0.158 | | |
| Fisher Exact Test (d) | | P=0.102 | P=0.181 |
| **Hematopoietic System: Malignant Lymphoma, Undifferentiated Type** | | | |
| Overall Rates (a) | 7/50 (14%) | 3/50 (6%) | 6/50 (12%) |
| Adjusted Rates (b) | 17.1% | 8.5% | 16.2% |
| Terminal Rates (c) | 2/33 (6%) | 2/33 (6%) | 6/37 (16%) |
| Week of First Observation | 91 | 97 | 105 |
| Life Table Tests (d) | P=0.385N | P=0.186N | P=0.441N |
| Incidental Tumor Tests (d) | P=0.472N | P=0.280N | P=0.536N |
| Cochran-Armitage Trend Test (d) | P=0.436N | | |
| Fisher Exact Test (d) | | P=0.159N | P=0.500N |
| **Hematopoietic System: Malignant Lymphoma, Lymphocytic Type** | | | |
| Overall Rates (a) | 3/50 (6%) | 0/50 (0%) | 0/50 (0%) |
| Adjusted Rates (b) | 7.9% | 0.0% | 0.0% |
| Terminal Rates (c) | 1/33 (3%) | 0/33 (0%) | 0/37 (0%) |
| Week of First Observation | 97 | | |
| Life Table Tests (d) | P=0.037N | P=0.132N | P=0.113N |
| Incidental Tumor Tests (d) | P=0.051N | P=0.159N | P=0.151N |
| Cochran-Armitage Trend Test (d) | P=0.037N | | |
| Fisher Exact Test (d) | | P=0.121N | P=0.121N |
| **Hematopoietic System: Malignant Lymphoma, Mixed Type** | | | |
| Overall Rates (a) | 1/50 (2%) | 5/50 (10%) | 4/50 (8%) |
| Adjusted Rates (b) | 3.0% | 13.6% | 9.8% |
| Terminal Rates (c) | 1/33 (3%) | 3/33 (9%) | 1/37 (3%) |
| Week of First Observation | 105 | 95 | 95 |
| Life Table Tests (d) | P=0.193 | P=0.103 | P=0.208 |
| Incidental Tumor Tests (d) | P=0.125 | P=0.082 | P=0.135 |
| Cochran-Armitage Trend Test (d) | P=0.158 | | |
| Fisher Exact Test (d) | | P=0.102 | P=0.181 |
| **Hematopoietic System: Lymphoma, All Malignant** | | | |
| Overall Rates (a) | 13/50 (26%) | 9/50 (18%) | 11/50 (22%) |
| Adjusted Rates (b) | 30.1% | 23.2% | 26.4% |
| Terminal Rates (c) | 4/33 (12%) | 5/33 (15%) | 7/37 (19%) |
| Week of First Observation | 91 | 74 | 72 |
| Life Table Tests (d) | P=0.307N | P=0.287N | P=0.347N |
| Incidental Tumor Tests (d) | P=0.480N | P=0.380N | P=0.555N |
| Cochran-Armitage Trend Test (d) | P=0.359N | | |
| Fisher Exact Test (d) | | P=0.235N | P=0.408N |

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Control | 2,500 ppm | 5,000 ppm |
|---|---|---|---|
| **Liver: Hepatocellular Adenoma** | | | |
| Overall Rates (a) | 2/50 (4%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted Rates (b) | 5.7% | 6.1% | 8.1% |
| Terminal Rates (c) | 1/33 (3%) | 2/33 (6%) | 3/37 (8%) |
| Week of First Observation | 102 | 105 | 105 |
| Life Table Tests (d) | P=0.454 | P=0.689 | P=0.546 |
| Incidental Tumor Tests (d) | P=0.430 | P=0.665 | P=0.513 |
| Cochran-Armitage Trend Test (d) | P=0.406 | | |
| Fisher Exact Test (d) | | P=0.691 | P=0.500 |
| **Liver: Hepatocellular Carcinoma** | | | |
| Overall Rates (a) | 3/50 (6%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted Rates (b) | 8.3% | 5.0% | 7.6% |
| Terminal Rates (c) | 2/33 (6%) | 0/33 (0%) | 2/37 (5%) |
| Week of First Observation | 97 | 68 | 97 |
| Life Table Tests (d) | P=0.552N | P=0.508N | P=0.622N |
| Incidental Tumor Tests (d) | P=0.535 | P=0.479N | P=0.649 |
| Cochran-Armitage Trend Test (d) | P=0.588 | | |
| Fisher Exact Test (d) | | P=0.500N | P=0.661 |
| **Liver: Hepatocellular Adenoma or Carcinoma** | | | |
| Overall Rates (a) | 5/50 (10%) | 4/50 (8%) | 6/50 (12%) |
| Adjusted Rates (b) | 13.7% | 10.7% | 15.5% |
| Terminal Rates (c) | 3/33 (9%) | 2/33 (6%) | 5/37 (14%) |
| Week of First Observation | 97 | 68 | 97 |
| Life Table Tests (d) | P=0.494 | P=0.510N | P=0.563 |
| Incidental Tumor Tests (d) | P=0.410 | P=0.506N | P=0.498 |
| Cochran-Armitage Trend Test (d) | P=0.434 | | |
| Fisher Exact Test (d) | | P=0.500N | P=0.500 |
| **Pituitary Gland: Adenoma** | | | |
| Overall Rates (a) | 3/39 (8%) | (e) 3/10 (30%) | 2/43 (5%) |
| Adjusted Rates (b) | 10.3% | | 6.1% |
| Terminal Rates (c) | 3/29 (10%) | | 2/33 (6%) |
| Week of First Observation | 105 | | 105 |
| Life Table Test (d) | | | P=0.441N |
| Incidental Tumor Test (d) | | | P=0.441N |
| Fisher Exact Test (d) | | | P=0.453N |
| **Uterus: Endometrial Stromal Polyp** | | | |
| Overall Rates (a) | 0/50 (0%) | (e) 0/31 (0%) | 3/49 (6%) |
| Adjusted Rates (b) | 0.0% | | 7.4% |
| Terminal Rates (c) | 0/33 (0%) | | 1/37 (3%) |
| Week of First Observation | | | 99 |
| Life Table Test (d) | | | P=0.139 |
| Incidental Tumor Test (d) | | | P=0.076 |
| Fisher Exact Test (d) | | | P=0.117 |

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *Skin | (50) | (50) | (50) |
| Inflammation, acute necrotizing | | 1 (2%) | |
| Inflammation, active chronic | | | 1 (2%) |
| *Subcutaneous tissue | (50) | (50) | (50) |
| Abscess, NOS | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| *Nasal cavity | (50) | (50) | (50) |
| Inflammation, acute | 3 (6%) | 1 (2%) | 1 (2%) |
| Inflammation, acute hemorrhagic | 1 (2%) | | |
| #Lung | (50) | (50) | (50) |
| Congestion, NOS | 1 (2%) | 1 (2%) | |
| Hemorrhage | 2 (4%) | 5 (10%) | 12 (24%) |
| Inflammation, acute | | 1 (2%) | 1 (2%) |
| Abscess, NOS | | 1 (2%) | 2 (4%) |
| Inflammation, chronic | 1 (2%) | | 1 (2%) |
| Bacterial septicemia | | 1 (2%) | |
| Hyperplasia, alveolar epithelium | 1 (2%) | 2 (4%) | |
| Histiocytosis | | 5 (10%) | 2 (4%) |
| HEMATOPOIETIC SYSTEM | | | |
| *Multiple organs | (50) | (50) | (50) |
| Leukemoid reaction | | 1 (2%) | |
| #Bone marrow | (49) | (9) | (49) |
| Myelofibrosis | 34 (69%) | 1 (11%) | 30 (61%) |
| Hyperplasia, hematopoietic | 1 (2%) | | |
| Hematopoiesis | | | 1 (2%) |
| #Spleen | (49) | (34) | (50) |
| Necrosis, NOS | 1 (2%) | | |
| Depletion, lymphoid | 3 (6%) | 4 (12%) | 4 (8%) |
| Hyperplasia, lymphoid | 4 (8%) | 5 (15%) | 9 (18%) |
| Hematopoiesis | 10 (20%) | 11 (32%) | 7 (14%) |
| #Lymph node | (47) | (22) | (46) |
| Abscess, NOS | 1 (2%) | 2 (9%) | |
| Hyperplasia, plasma cell | | 1 (5%) | |
| #Mandibular lymph node | (47) | (22) | (46) |
| Inflammation, acute | | | 1 (2%) |
| Depletion, lymphoid | | 1 (5%) | |
| Hyperplasia, plasma cell | | | 1 (2%) |
| Hyperplasia, lymphoid | | | 2 (4%) |
| #Mediastinal lymph node | (47) | (22) | (46) |
| Inflammation, acute | 1 (2%) | 1 (5%) | |
| Abscess, NOS | 1 (2%) | 2 (9%) | |
| Inflammation, active chronic | 1 (2%) | | |
| Depletion, lymphoid | 1 (2%) | | |
| Angiectasis | | | 1 (2%) |
| Hyperplasia, plasma cell | 2 (4%) | 1 (5%) | 1 (2%) |
| Hyperplasia, lymphoid | 1 (2%) | | |
| #Pancreatic lymph node | (47) | (22) | (46) |
| Pigmentation, NOS | | 1 (5%) | |
| Depletion, lymphoid | | 2 (9%) | |
| Hyperplasia, reticulum cell | | 1 (5%) | |

**TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)**

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| HEMATOPOIETIC SYSTEM (Continued) | | | |
| #Lumbar lymph node | (47) | (22) | (46) |
| Hemorrhage | | | 1 (2%) |
| Inflammation, active chronic | 1 (2%) | | |
| Necrosis, coagulative | | | 1 (2%) |
| Hyperplasia, plasma cell | | | 2 (4%) |
| Hyperplasia, lymphoid | 1 (2%) | 1 (5%) | |
| #Mesenteric lymph node | (47) | (22) | (46) |
| Hemorrhage | 1 (2%) | | |
| Abscess, NOS | | 1 (5%) | |
| Depletion, lymphoid | 3 (6%) | | |
| Angiectasis | 3 (6%) | | 2 (4%) |
| Hyperplasia, lymphoid | 2 (4%) | 2 (9%) | 2 (4%) |
| #Renal lymph node | (47) | (22) | (46) |
| Abscess, NOS | | 1 (5%) | |
| Hyperplasia, plasma cell | 1 (2%) | 2 (9%) | 1 (2%) |
| Hyperplasia, lymphoid | | 1 (5%) | |
| #Pelvic lymph node | (47) | (22) | (46) |
| Hemorrhage | 1 (2%) | | |
| Necrosis, NOS | 1 (2%) | | |
| #Inguinal lymph node | (47) | (22) | (46) |
| Hyperplasia, plasma cell | 1 (2%) | | |
| #Lung | (50) | (50) | (50) |
| Leukemoid reaction | | 1 (2%) | 1 (2%) |
| #Liver | (50) | (50) | (50) |
| Leukemoid reaction | 1 (2%) | | 1 (2%) |
| Hematopoiesis | 3 (6%) | 5 (10%) | 2 (4%) |
| #Peyer's patch | (49) | (12) | (50) |
| Hyperplasia, lymphoid | 2 (4%) | 3 (25%) | 1 (2%) |
| #Adrenal cortex | (48) | (9) | (48) |
| Hematopoiesis | | | 1 (2%) |
| #Thymus | (38) | (6) | (36) |
| Cyst, NOS | 8 (21%) | 1 (17%) | 5 (14%) |
| Hemorrhage | | | 1 (3%) |
| Depletion, lymphoid | 3 (8%) | 2 (33%) | 2 (6%) |
| Angiectasis | | | 1 (3%) |
| Plasmacytosis | 1 (3%) | | |
| Hyperplasia, lymphoid | 1 (3%) | 1 (17%) | |
| CIRCULATORY SYSTEM | | | |
| #Brain | (50) | (49) | (50) |
| Perivasculitis | | | 1 (2%) |
| *Mediastinum | (50) | (50) | (50) |
| Perivasculitis | 1 (2%) | | |
| #Mesenteric lymph node | (47) | (22) | (46) |
| Thrombus, organized | 1 (2%) | | |
| #Lung | (50) | (50) | (50) |
| Perivasculitis | 2 (4%) | 3 (6%) | 4 (8%) |
| #Heart | (50) | (9) | (50) |
| Mineralization | 1 (2%) | | |
| Thrombus, mural | | | 1 (2%) |
| Inflammation, acute | 1 (2%) | | |
| Abscess, NOS | 1 (2%) | | |
| Inflammation, chronic | 2 (4%) | | |
| Fibrosis, focal | 3 (6%) | | 1 (2%) |
| Perivasculitis | 2 (4%) | | |
| Bacterial septicemia | | | 1 (2%) |
| Necrosis, coagulative | 1 (2%) | | |

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| CIRCULATORY SYSTEM (Continued) | | | |
| *Pulmonary artery | (50) | (50) | (50) |
| Mineralization | | 3 (6%) | |
| Thrombus, organized | 1 (2%) | | |
| Inflammation, chronic | | 1 (2%) | |
| Perivasculitis | | 3 (6%) | |
| Hyperplasia, NOS | | 2 (4%) | |
| #Salivary gland | (47) | (9) | (43) |
| Perivasculitis | | | 1 (2%) |
| #Liver | (50) | (50) | (50) |
| Thrombosis, NOS | | | 1 (2%) |
| #Uterus | (50) | (31) | (49) |
| Thrombosis, NOS | | | 1 (2%) |
| #Ovary/parovarian | (49) | (50) | (45) |
| Thrombosis, NOS | | | 1 (2%) |
| #Ovary | (49) | (50) | (45) |
| Thrombosis, NOS | | 1 (2%) | |
| DIGESTIVE SYSTEM | | | |
| #Salivary gland | (47) | (9) | (43) |
| Mineralization | | | 1 (2%) |
| Inflammation, NOS | | 1 (11%) | |
| Abscess, NOS | | | 1 (2%) |
| Inflammation, chronic | 34 (72%) | 4 (44%) | 29 (67%) |
| Necrosis, fibrinoid | | | 1 (2%) |
| #Liver | (50) | (50) | (50) |
| Mineralization | | | 1 (2%) |
| Cyst, NOS | 1 (2%) | | |
| Congestion, NOS | | 1 (2%) | |
| Hemorrhage | | 1 (2%) | |
| Inflammation, active chronic | 9 (18%) | 13 (26%) | 3 (6%) |
| Inflammation, chronic | 7 (14%) | 13 (26%) | 6 (12%) |
| Necrosis, coagulative | 16 (32%) | 11 (22%) | 5 (10%) |
| Nuclear enlargement | | | 1 (2%) |
| Cytoplasmic vacuolization | | 1 (2%) | 2 (4%) |
| Basophilic cyto change | | | 2 (4%) |
| Clear cell change | 3 (6%) | | 1 (2%) |
| Hepatocytomegaly | | 1 (2%) | 1 (2%) |
| Angiectasis | 1 (2%) | 1 (2%) | 1 (2%) |
| #Liver/periportal | (50) | (50) | (50) |
| Inflammation, chronic | | | 4 (8%) |
| #Liver/Kupffer cell | (50) | (50) | (50) |
| Hyperplasia, NOS | | 2 (4%) | |
| *Gallbladder | (50) | (50) | (50) |
| Inflammation, chronic | | 1 (2%) | |
| #Bile duct | (50) | (50) | (50) |
| Inflammation, chronic | | 1 (2%) | |
| #Pancreas | (50) | (11) | (50) |
| Dilatation/ducts | 1 (2%) | 1 (9%) | |
| Hemorrhagic cyst | 1 (2%) | | |
| Inflammation, NOS | | 1 (9%) | |
| Inflammation, active chronic | 4 (8%) | | 1 (2%) |
| Inflammation, chronic | 39 (78%) | 2 (18%) | 42 (84%) |
| Fibrosis | 1 (2%) | | |
| Adhesion, NOS | 1 (2%) | | |
| Cytoplasmic change, NOS | 1 (2%) | | |
| Atrophy, NOS | 3 (6%) | 1 (9%) | 3 (6%) |
| Hyperplasia, NOS | | | 1 (2%) |
| #Glandular stomach | (50) | (16) | (50) |
| Mineralization | 1 (2%) | | |
| Cyst, NOS | 1 (2%) | | 2 (4%) |
| Inflammation, chronic | 5 (10%) | 3 (19%) | 4 (8%) |

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| DIGESTIVE SYSTEM (Continued) | | | |
| #Forestomach | (50) | (16) | (50) |
| Ulcer | | | 1 (2%) |
| Inflammation, acute | | 2 (13%) | 2 (4%) |
| Inflammation, chronic | 5 (10%) | 3 (19%) | 2 (4%) |
| Hyperplasia, epithelial | 1 (2%) | | |
| Hyperplasia, basal cell | | 2 (13%) | |
| Hyperkeratosis | 2 (4%) | 3 (19%) | 3 (6%) |
| Acanthosis | 5 (10%) | 3 (19%) | 7 (14%) |
| Angiectasis | 1 (2%) | | |
| #Duodenum | (49) | (12) | (50) |
| Hyperplasia, epithelial | 1 (2%) | | |
| #Jejunum | (49) | (12) | (50) |
| Inflammation, active chronic | 1 (2%) | | |
| Necrosis, NOS | 1 (2%) | | |
| #Colon | (50) | (9) | (50) |
| Inflammation, acute | 1 (2%) | | |
| Parasitism | 2 (4%) | | |
| Necrosis, NOS | 1 (2%) | | |
| Hyperplasia, epithelial | 1 (2%) | | |
| URINARY SYSTEM | | | |
| #Kidney | (50) | (17) | (50) |
| Cyst, NOS | | | 1 (2%) |
| Glomerulonephritis, NOS | 6 (12%) | 2 (12%) | 7 (14%) |
| Pyelonephritis, NOS | 1 (2%) | | 1 (2%) |
| Inflammation, NOS | | 1 (6%) | |
| Abscess, NOS | | | 1 (2%) |
| Inflammation, chronic | 43 (86%) | 10 (59%) | 43 (86%) |
| Glomerulosclerosis, NOS | 2 (4%) | 1 (6%) | 1 (2%) |
| Pigmentation, NOS | | 1 (6%) | |
| #Kidney/tubule | (50) | (17) | (50) |
| Mineralization | 2 (4%) | | 1 (2%) |
| Dilatation, NOS | | | 1 (2%) |
| Atrophy, NOS | 1 (2%) | | 1 (2%) |
| Regeneration, NOS | 6 (12%) | 1 (6%) | 10 (20%) |
| #Urinary bladder | (50) | (8) | (49) |
| Inflammation, NOS | | 1 (13%) | |
| Inflammation, chronic | 32 (64%) | | 34 (69%) |
| Fibrosis | 1 (2%) | | |
| ENDOCRINE SYSTEM | | | |
| #Anterior pituitary | (39) | (10) | (43) |
| Cyst, NOS | 1 (3%) | | 2 (5%) |
| Hyperplasia, NOS | 4 (10%) | | 8 (19%) |
| Angiectasis | 1 (3%) | | |
| #Adrenal | (48) | (9) | (48) |
| Angiectasis | 5 (10%) | | 1 (2%) |
| #Adrenal cortex | (48) | (9) | (48) |
| Metamorphosis, fatty | 1 (2%) | | |
| Hyperplasia, focal | | | 1 (2%) |
| #Adrenal medulla | (48) | (9) | (48) |
| Hyperplasia, NOS | 1 (2%) | | |
| #Thyroid | (45) | (8) | (47) |
| Inflammation, chronic | 1 (2%) | | 2 (4%) |
| Hyperplasia, follicular cell | 1 (2%) | | 2 (4%) |

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| REPRODUCTIVE SYSTEM | | | |
| *Mammary gland | (50) | (50) | (50) |
| Hyperplasia, NOS | | | 1 (2%) |
| *Fallopian tube lumen | (50) | (50) | (50) |
| Inflammation, active chronic | | 1 (2%) | |
| *Clitoral gland | (50) | (50) | (50) |
| Dilatation/ducts | | | 2 (4%) |
| Inflammation, active chronic | | 1 (2%) | 2 (4%) |
| *Vagina | (50) | (50) | (50) |
| Polyp, NOS | | | 1 (2%) |
| #Uterus | (50) | (31) | (49) |
| Hydrometra | 2 (4%) | 5 (16%) | |
| Cyst, NOS | | 1 (3%) | |
| Inflammation, acute | 10 (20%) | 2 (6%) | 7 (14%) |
| Abscess, NOS | | 1 (3%) | |
| Angiectasis | 1 (2%) | | |
| #Cervix uteri | (50) | (31) | (49) |
| Inflammation, acute | 1 (2%) | | |
| #Uterus/endometrium | (50) | (31) | (49) |
| Inflammation, active chronic | | | 1 (2%) |
| Hyperplasia, NOS | 45 (90%) | 20 (65%) | 45 (92%) |
| Metaplasia, squamous | | 1 (3%) | |
| #Fallopian tube | (50) | (31) | (49) |
| Inflammation, acute | | 2 (6%) | |
| #Ovary/parovarian | (49) | (50) | (45) |
| Mineralization | 2 (4%) | | |
| Abscess, NOS | 6 (12%) | 5 (10%) | 1 (2%) |
| Inflammation, chronic | 9 (18%) | 23 (46%) | 6 (13%) |
| Adhesion, NOS | | 1 (2%) | |
| #Ovary | (49) | (50) | (45) |
| Cyst, NOS | 4 (8%) | 7 (14%) | 10 (22%) |
| Parovarian cyst | 7 (14%) | 4 (8%) | 5 (11%) |
| Hemorrhagic cyst | 6 (12%) | 10 (20%) | 4 (9%) |
| Pigmentation, NOS | | 1 (2%) | |
| Atrophy, NOS | | | 1 (2%) |
| Angiectasis | 2 (4%) | 1 (2%) | |
| NERVOUS SYSTEM | | | |
| *Choroid plexus | (50) | (50) | (50) |
| Inflammation, chronic | | | 1 (2%) |
| #Brain | (50) | (49) | (50) |
| Hemorrhage | 1 (2%) | | |
| #Brain/thalamus | (50) | (49) | (50) |
| Mineralization | 40 (80%) | 33 (67%) | 31 (62%) |
| SPECIAL SENSE ORGANS | | | |
| *Eye/cornea | (50) | (50) | (50) |
| Inflammation, active chronic | | | 1 (2%) |
| *Nasolacrimal duct | (50) | (50) | (50) |
| Inflammation, NOS | 3 (6%) | 2 (4%) | 4 (8%) |
| *Harderian gland | (50) | (50) | (50) |
| Cyst, NOS | | | 1 (2%) |
| Inflammation, active chronic | | | 1 (2%) |
| Inflammation, chronic | 1 (2%) | | |
| Hyperplasia, NOS | 1 (2%) | | |

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID (Continued)

| | Untreated Control | Low Dose | High Dose |
|---|---|---|---|
| MUSCULOSKELETAL SYSTEM | | | |
| *Intercostal muscle | (50) | (50) | (50) |
| Inflammation, acute | 4 (8%) | 2 (4%) | 1 (2%) |
| Abscess, NOS | | 1 (2%) | |
| BODY CAVITIES | | | |
| *Thoracic cavity | (50) | (50) | (50) |
| Hemothorax | 1 (2%) | | |
| *Mediastinum | (50) | (50) | (50) |
| Inflammation, active chronic | | | 1 (2%) |
| *Peritoneum | (50) | (50) | (50) |
| Inflammation, NOS | 4 (8%) | 3 (6%) | 2 (4%) |
| Inflammation, acute | 1 (2%) | | |
| *Peritoneal cavity | (50) | (50) | (50) |
| Hemoperitoneum | | 1 (2%) | |
| *Pleura | (50) | (50) | (50) |
| Inflammation, acute | 1 (2%) | | 1 (2%) |
| *Pericardial cavity | (50) | (50) | (50) |
| Hemopericardium | 1 (2%) | | |
| *Mesentery | (50) | (50) | (50) |
| Abscess, NOS | 1 (2%) | | |
| Inflammation, active chronic | 1 (2%) | | |
| ALL OTHER SYSTEMS | | | |
| *Multiple organs | (50) | (50) | (50) |
| Inflammation, NOS | 1 (2%) | 1 (2%) | |
| Inflammation, acute/chronic | 1 (2%) | | |
| Bacterial septicemia | | | 1 (2%) |
| Omentum | | | |
| Inflammation, acute | 1 | | |
| Inflammation, active chronic | 2 | | |
| Fibrosis | 1 | | |
| Necrosis, NOS | 1 | | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| None | | | |

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

# APPENDIX C

# GENETIC TOXICOLOGY OF BORIC ACID

TABLE C1. MUTAGENICITY OF BORIC ACID IN *SALMONELLA TYPHIMURIUM*

| Strain | Dose (µg/plate) | Revertants/plate (a,b) | | |
|---|---|---|---|---|
| | | −S9 | +S9 (rat) | +S9 (hamster) |
| TA100 | 0 | 85 ± 7.0 | 116 ± 5.2 | 122 ± 8.8 |
| | 33 | 72 ± 2.3 | 133 ± 3.7 | 116 ± 12.3 |
| | 100 | 79 ± 7.0 | 132 ± 3.8 | 127 ± 10.5 |
| | 333 | 75 ± 3.4 | 127 ± 3.2 | 131 ± 14.2 |
| | 1,000 | 101 ± 3.5 | 139 ± 8.7 | 137 ± 13.1 |
| | 1,820 | 106 ± 3.1 | 127 ± 6.9 | 158 ± 6.1 |
| TA1535 | 0 | 5 ± 0.6 | 7 ± 0.9 | 7 ± 2.5 |
| | 33 | 6 ± 0.9 | 8 ± 1.9 | 7 ± 2.3 |
| | 100 | 6 ± 1.2 | 13 ± 2.0 | 10 ± 2.0 |
| | 333 | 5 ± 1.9 | 8 ± 1.8 | 5 ± 1.2 |
| | 1,000 | 5 ± 1.5 | 6 ± 2.1 | 8 ± 0.3 |
| | 1,820 | 7 ± 2.1 | 6 ± 0.7 | 8 ± 1.8 |
| TA1537 | 0 | 3 ± 0.3 | 6 ± 0.5 | 6 ± 0.6 |
| | 33 | 4 ± 0.6 | 5 ± 0.6 | 5 ± 0.7 |
| | 100 | 4 ± 0.0 | 4 ± 1.2 | 6 ± 1.0 |
| | 333 | 2 ± 0.3 | 4 ± 0.3 | 6 ± 1.5 |
| | 1,000 | 3 ± 0.7 | 3 ± 1.5 | 5 ± 0.7 |
| | 1,820 | 1 ± 0.3 | 5 ± 1.5 | 3 ± 0.3 |
| TA98 | 0 | 14 ± 4.6 | 19 ± 3.8 | 19 ± 2.6 |
| | 33 | 13 ± 1.0 | 22 ± 2.3 | 22 ± 0.9 |
| | 100 | 9 ± 3.2 | 24 ± 1.2 | 21 ± 2.6 |
| | 333 | 13 ± 1.2 | 28 ± 1.9 | 21 ± 1.5 |
| | 1,000 | 14 ± 2.2 | 24 ± 1.2 | 22 ± 3.3 |
| | 1,820 | 16 ± 1.5 | 22 ± 3.2 | 24 ± 2.2 |

(a) The S9 fractions were prepared from the liver of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or solvent were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error

TABLE C2. MUTAGENICITY OF BORIC ACID IN L5178Y MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

| Compound | Dose (μg/ml) | Total Mutant Clones | Cloning Efficiency (percent) | Relative Total Growth (percent) | Mutation Frequency (mutants/$10^6$ clonable cells) |
|---|---|---|---|---|---|
| FOP-Fischer medium | | | | | |
| | 0 | 83 | 88.5 | 123 | 31 |
| | | 70 | 59.5 | 108 | 39 |
| | | 72 | 75.5 | 86 | 32 |
| | | 83 | 78.5 | 83 | (b) 35 (34) |
| Methyl methanesulfonate | | | | | |
| | 15 | 225 | 20.5 | 16.8 | 367 |
| | | 257 | 21.3 | 17.8 | 402 (385) |
| Boric acid | | | | | |
| | 1,000 | 83 | 71.8 | 104.5 | 39 |
| | | 79 | 69.7 | 108.7 | 38 (38) |
| | 1,800 | 97 | 89.0 | 94.4 | 36 |
| | | 81 | 75.0 | 91.9 | 36 (36) |
| | 2,600 | 90 | 73.3 | 102.5 | 41 |
| | | 90 | 71.3 | 87.1 | 42 (41) |
| | 3,400 | 100 | 91.2 | 82.4 | 37 |
| | | 130 | 88.0 | 90.3 | 49 (43) |
| | 4,200 | 146 | 98.7 | 85.6 | 49 |
| | | 150 | 107.2 | 83.9 | 47 (48) |
| | 5,000 | 160 | 95.0 | 78.9 | 56 |
| | | 135 | 102.7 | 88.7 | 44 (50) |

(a) Experiments were performed twice, and all doses were tested in duplicate or quadruplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells ($6 \times 10^5$/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, $3 \times 10^6$ cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.
(b) The mean is given in parentheses.

TABLE C3. MUTAGENICITY OF BORIC ACID IN L5178Y MOUSE LYMPHOMA CELLS IN THE PRESENCE OF S9 (a)

| Compound | Dose (μg/ml) | Total Mutant Clones | Cloning Efficiency (percent) | Relative Total Growth (percent) | Mutation Frequency (mutants/$10^6$ clonable cells) |
|---|---|---|---|---|---|
| FOP-Fischer medium | | | | | |
| | | 222 | 80.2 | 106 | 92 |
| | | 285 | 96.2 | 103 | 99 |
| | | 223 | 87.2 | 102 | 85 |
| | | 175 | 69.5 | 87 | (b) 84 (90) |
| Methylcholanthrene | | | | | |
| | 2.5 | 787 | 45.0 | 37.5 | 583 |
| | | 867 | 59.2 | 33.8 | 488 (536) |
| Boric acid | | | | | |
| | 1,000 | 176 | 72.5 | 89.9 | 81 |
| | | 211 | 83.3 | 99.1 | 84 (83) |
| | 2,000 | 235 | 80.2 | 87.6 | 98 |
| | | 278 | 93.7 | 89.9 | 99 (98) |
| | 3,000 | 257 | 80.3 | 99.8 | 107 |
| | | 263 | 79.3 | 71.2 | 111 (109) |
| | 4,000 | 273 | 99.7 | 77.1 | 91 |
| | | 217 | 73.3 | 87.3 | 99 (95) |
| | 5,000 | 230 | 56.5 | 65.0 | 136 |
| | | 175 | 63.8 | 56.6 | 91 (114) |

(a) Experiments were performed twice, and all doses were tested in duplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells ($6 \times 10^5$/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, $3 \times 10^6$ cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells. S9 was prepared from the liver of Aroclor 1254-induced male F344 rats.
(b) The mean is given in parentheses.

TABLE C4. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY BORIC ACID (a)

| −S9 (b) | | +S9 (c) | |
|---|---|---|---|
| Dose (μg/ml) | SCE/Cell | Dose (μg/ml) | SCE/Cell |
| Medium | 8.4 | Medium | 8.6 |
| DMSO | 9.2 | DMSO | 10.3 |
| Boric acid | | Boric acid | |
| 200 | 7.7 | 250 | 9.7 |
| 300 | 9.6 | 500 | 9.7 |
| 400 | 9.7 | 1,600 | 9.8 |
| 500 | 10.1 | 2,000 | 9.8 |
| Mitomycin C | | Cyclophosphamide | |
| 0.001 | 25.6 | 0.300 | 12.7 |
| 0.010 | 76.7 | 2.000 | 31.2 |

(a) SCE, sister-chromatid exchange
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent at 37° C; 2 hours after initiation of treatment, 10 μM BrdU was added, and incubation continued for an additional 22-24 hours. Cells were washed, fresh medium containing BrdU (10 μM) and colcemid (0.1 μg/ml) was added, and incubation was continued for 2-3 hours (Galloway et al., 1985).
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 μM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 μg/ml) present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).

TABLE C5. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY BORIC ACID (a)

| −S9 (b) | | +S9 (c) | |
|---|---|---|---|
| Dose (μg/ml) | Abs/100 Cells (percent cells with abs) | Dose (μg/ml) | Abs/100 Cells (percent cells with abs) |
| Medium | 3 (3) | Medium | 2 (2) |
| DMSO | 3 (3) | DMSO | 0 (0) |
| Boric acid | | Boric acid | |
| 500 | 2 (1) | 1,000 | 2 (2) |
| 1,000 | 6 (5) | 1,600 | 4 (3) |
| 1,500 | 2 (2) | 2,000 | 1 (1) |
| 2,000 | 3 (3) | 2,500 | 5 (5) |
| Mitomycin C | | Cyclophosphamide | |
| 0.250 | 56 (38) | 15 | 24 (22) |
| 1.000 | 94 (60) | 50 | 118 (72) |

(a) Abs, aberrations
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 μg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa (Galloway et al., 1985).
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid (0.1 μg/ml) was added for the last 2-3 hours of incubation; then cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).

# APPENDIX D

# CHEMICAL CHARACTERIZATION OF BORIC ACID

# APPENDIX D. CHEMICAL CHARACTERIZATION

## I. Identity and Purity Determinations of Boric Acid Lot No. 051479 Performed by the Analytical Chemistry Laboratory

| A. Physical properties | Determined | Literature Values |
|---|---|---|
| 1. Appearance: | Colorless, crystalline solid | Colorless crystals (Merck Index, 1973) |
| 2. Melting point: | Solid DSC (DuPont 900) indicates two irregularly shaped unresolved endotherms. The first was from 98.2° to 139.0° C and the second from 151.2° to 165.8° C. | Approximately 171° C (Merck Index, 1973) |
| **B. Spectral data** | | |
| 1. Infrared | | |
| Instrument: | Beckman IR-12 | |
| Phase: | Potassium bromide pellet | |
| Results: | See Figure 3 | Identical with literature spectrum (Sadtler Standard Spectra) |
| 2. Ultraviolet/visible | | |
| Instrument: | Cary 118 | |
| Results: | A 1% (w/v) solution in water exhibited no absorbance between 800 and 220 nm. | No literature spectrum; consistent with structure. |

**C. Titration**

1. **Procedure:** Titration of one proton, after increasing the acidity of the compound by complexation with glycerol, with 0.1 N aqueous sodium hydroxide (USP, 1965)

2. **Results:** 99.7% ± 0.2(δ)%.

**D. Weight loss on drying over silica gel:** 0.03%

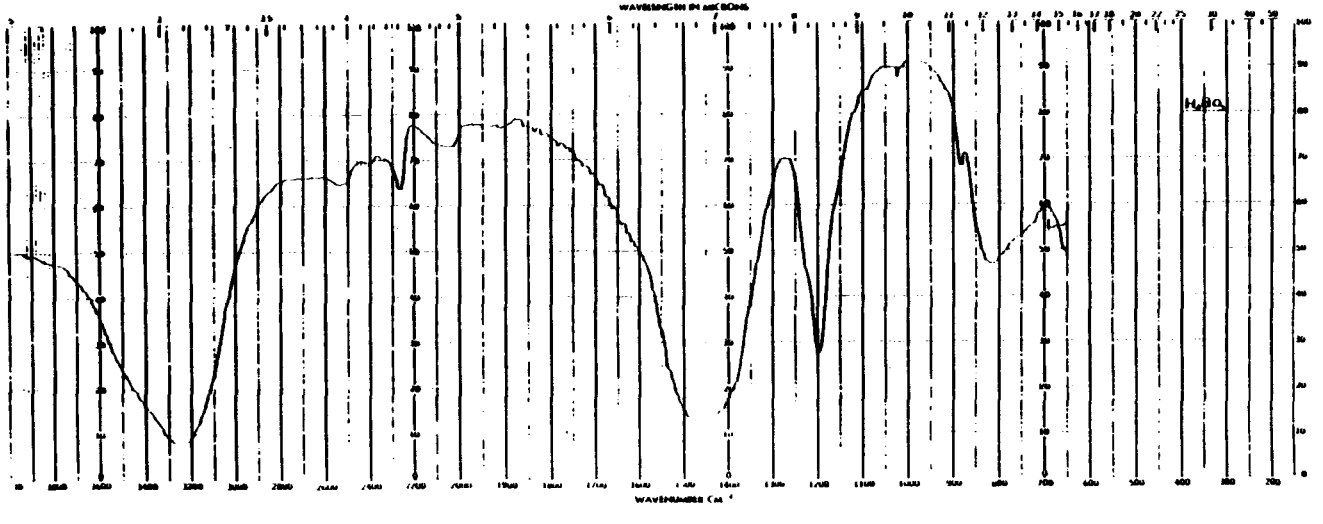

**FIGURE 3. INFRARED ABSORPTION SPECTRUM OF BORIC ACID (LOT NO. 051479)**

**E. Elemental analysis**

| Element | B |
|---|---|
| Theory (T) | 17.50 |
| Determined (D) | 17.51<br>17.67 |
| Percent D/T | 100.5 |

**F. Spark source mass spectrometry (μg/μl)**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Uranium | 7.0 | Terbium | <0.24 | Ruthenium | <1.1 | Vanadium | NR |
| Thorium | <1.2 | Gadolinium | <1.0 | Molybdenum | 2.8 | Titanium | 1.6 |
| Bismuth | <1.2 | Europium | <0.47 | Niobium | <0.48 | Scandium | <0.54 |
| Lead | <2.5 | Samarium | <1.6 | Zirconium | <0.30 | Calcium | 66 |
| Thallium | <1.2 | Neodymium | <1.8 | Yttrium | <0.22 | Potassium | ≈1,600 |
| Mercury | NR | Praseodymium | <0.54 | Strontium | <0.69 | Chlorine | 34 |
| Gold | <0.63 | Cerium | <0.29 | Rubidium | 4.2 | Sulfur | 56 |
| Platinum | <1.9 | Lanthanum | <0.41 | Bromine | <1.2 | Phosphorus | 6.0 |
| Iridium | <0.98 | Barium | 1.1 | Selenium | <0.94 | Silicon | ≈1,800 |
| Osmium | <1.5 | Cesium | <0.15 | Arsenic | <1.2 | Aluminum | 200 |
| Rhenium | Internal Standard | Iodine | <0.44 | Germanium | <0.25 | Magnesium | 1.4 |
| Tungsten | <1.6 | Tellurium | NR | Gallium | NR | Sodium | 112 |
| Tantalum | 1.8 | Antimony | 0.92 | Zinc | 0.29 | Fluorine | 26 |
| Hafnium | <2.4 | Tin | <0.58 | Copper | 0.25 | Oxygen | NR |
| Lutetium | <0.17 | Indium | Internal Standard | Nickel | NR | Nitrogen | NR |
| Ytterbium | <0.99 | Cadmium | <0.36 | Cobalt | NR | Carbon | NR |
| Thulium | <0.39 | Silver | <0.18 | Iron | 15 | Boron | Major |
| Erbium | <1.3 | Palladium | <1.2 | Manganese | NR | Beryllium | 6.0 |
| Holmium | <0.20 | Rhodium | <0.33 | Chromium | 0.19 | Lithium | NR |
| Dysprosium | <0.27 | | | | | | |

**G. Conclusions:** The elemental analysis value for boron agreed with the theoretical value. Spark source mass spectrometry indicated the presence of two significant metal impurities, silicon (approximately 0.18%) and potassium (approximately 0.16%). The weight loss on drying was 0.03%. Titration with 0.1 N sodium hydroxide indicated a purity of 99.7% ± 0.2(δ)%. The infrared spectrum was identical to a literature spectrum. The ultraviolet/visible spectra was consistent with the structure.

## II. Stability Study of Boric Acid Lot No. 051479 Performed by the Analytical Chemistry Laboratory

**A. Sample storage:** Samples were stored in glass containers with Teflon®-lined caps in the dark for 2 weeks at temperatures of – 20°, 5°, 25°, or 60° C.

**B. Analytical method:** Triplicate (2-g) samples from each storage temperature were analyzed by the titrimetric method detailed in Section I.C.1. of this appendix.

**C. Results**

| Storage Temperature | Percent Compound (normalized to – 20° C sample) |
|---|---|
| – 20° C | 100.0 ± 0.1 |
| 5° C | 100.1 ± 0.1 |
| 25° C | 100.2 ± 0.1 |
| 60° C | 100.1 ± 0.1 |

**D. Conclusions:** Boric acid, as the bulk chemical and within the limits of error of the analysis, is stable at temperatures of up to 60° C for 2 weeks when stored as described above.

## III. Stability of Boric Acid Lot. No. 051479 at the Study Laboratory

### A. Storage conditions

**Bulk:** 4° C until 12/03/79; then 0° ± 5° C until 03/11/81; then 23° C until 08/03/81; then 0° C
**Reference:** −18° C or lower

### B. Analytical method

1. **Infrared spectroscopy**

   **Instrument:** Perkin-Elmer Infracord #137
   **Phase:** Potassium bromide pellet

2. **Titration:** Titration of 2 g of boric acid to phenolphthalein endpoint with standardized 1 N aqueous sodium hydroxide after complexing with neutralized glycerol:water (1:1)

### C. Results

1. **Infrared spectroscopy:** All bulk and reference spectra were comparable to the spectrum supplied by the analytical chemistry laboratory.

2. **Titration**

| Date of Analysis | Percent Purity (a) | |
|---|---|---|
| | Bulk | Reference |
| 09/27/79 | 99.7 | -- |
| 12/20/79 | 99.6 | 99.4 |
| 04/28/80 | 99.7 | 99.6 |
| 08/01/80 | 99.8 | 100.2 |
| 12/24/80 | 99.3 | 99.1 |
| 03/30/81 | 99.6 | 99.7 |
| 05/04/81 | 99.6 | 99.6 |
| 08/12/81 | 99.5 | 99.6 |
| 12/11/81 | 99.4 | 99.6 |

(a) Results of duplicate analysis

### D. Conclusion: No notable degradation occurred throughout the studies.

# APPENDIX E

# PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

## I. Studies Conducted by the Analytical Chemistry Laboratory

### A. Analysis of formulated diets for mixing homogeneity

1. **Premix preparation:** Boric acid (1.500 g) was transferred to a tared 600-ml beaker and thoroughly mixed by spatula with approximately 2 g of feed. More feed was added in 5-, 20-, and 50-g amounts with mixing between additions. The last addition of feed brought the total premix weight to 200 g. The concentration of boric acid in the finished premix was 7,500 ppm.

2. **Bulk mixing and sampling:** A 600-g portion of feed was layered evenly in the blender; then the 200-g premix was added in roughly equal amounts to both sides of the blender. The fine material adhering to the beaker walls was taken up by stirring 100 g of feed in the beaker briefly and then adding the feed to the blender. After an additional 600 g of feed was layered over the premix, the blender ports were sealed.

   Blending was conducted with the intensifier bar on for the first 5 minutes of mixing. At the end of the 15-minute mixing period, approximately 50 g was sampled from the upper right- and left-hand shells and from the bottom discharge port.

   Triplicate 10-g (±0.01 g) portions of each sample were transferred to individual 200-ml centrifuge bottles for analysis. The target concentration of boric acid in the final blend was 1,000 ppm.

3. **Analysis procedure**

   a. **Special reagents**

      Hydrochloric acid, 20% v/v, aqueous
      Curcumin reagent, 25 mg of curcumin (Eastman crystalline grade, dissolved in 100 ml of 95% ethanol)
      Oxalic acid solution, 10 g/100 ml in acetone

   b. **Procedure:** Samples (10.0 g in 200-ml centrifuge bottles) were extracted with 100 ml of reagent-grade methanol by shaking for 15 minutes on a Burrell Wrist-Action® shaker. The extracts were clarified by centrifuging and decanted carefully into individual 200-ml volumetric flasks.

      The feed residue in the bottles was re-extracted with 100 ml of methanol as above, and the extract was decanted as completely as possible into the flask containing the first extract. The feed residue was discarded. The combined extracts were diluted to 200 ml with methanol and thoroughly mixed, and then a 10-ml aliquot of each solution was further diluted to 50 ml with methanol and mixed.

      An aliquot (1 ml) of the diluted extract was pipetted into a 100-ml round-bottom flask with a 24/40 neck joint and was mixed with the following reagents added in order:

      1 ml hydrochloric acid 20%
      2 ml curcumin reagent
      5 ml oxalic acid solution

The flask was connected to a rotary vacuum evaporator equipped with an 80° C water bath. Immediately after the flask was connected, the motor speed was set at approximately 80 rpm and a vacuum was drawn with a water aspirator to maintain approximately 30 mm pressure for 8 minutes.

At the end of the 8-minute evaporation-reaction period, the flask was disconnected and cooled briefly in a water bath (approximately 15° C). Acetone (25 ml) was pipetted into the flask that was then stoppered tightly to prevent evaporation. The contents were dissolved by swirling. The solution was allowed to stand for approximately 5 minutes; then about 10-15 ml was filtered by syringe through a 0.5-µ Millipore filter and sealed in a 25-ml flask with a glass stopper. The solution was kept in the dark until the absorbance was measured at 537 nm in a 1-cm cell on a Carey 118 spectrophotometer. The reference cell contained a reagent blank solution prepared by treating 1 ml of methanol like the sample.

A standard curve was prepared with each set of samples using boric acid solutions in methanol at concentrations of 0, 5, 10, and 15 µg/ml. The final sample solutions were protected from light; absorbance readings were made within 30-35 minutes after the dry residue was dissolved.

4. **Quality assurance measures:** All samples were analyzed in duplicate using duplicate color developments on each extract. No correction was applied to the sample absorbance readings (approximately 0.400) for a feed blank because the blank feed absorbance was less than 0.002 AU. The zero-time spiked feed recovery, determined in triplicate, was 84.9% ± 2.2% and was applied to the sample results. The spiked feed samples were prepared by duplicate extractions of 50-g portions of feed containing 50.0 mg of boric acid with 500-ml portions of methanol and diluting to 1,000 ml.

   The linearity of the spectrophotometric curve was evaluated with standard solutions of boric acid in methanol at concentrations of 0, 5, 10, and 15 µg/ml. The linear correlation coefficient was 0.99999. The sample results were calculated from the linear regression equation developed from the standard curve data.

5. **Results**

| Sampling Location | Boric Acid Found (ppm) (a,b) |
|---|---|
| Left | 968 ± 4 |
| Right | 978 ± 2 |
| Bottom | 986 ± 1 |

(a) Results are the mean of duplicate analysis corrected for zero-time recovery yield of 84.9% ± 2.16%.
(b) The target concentration of the samples was 1,000 ppm.

6. **Conclusions:** Boric acid was blended into rodent feed at 1,000 ppm with a variability of ± 1% from the mean concentration of the blend.

**B. Analysis of formulated diet for stability of boric acid**

1. **Sample preparation and storage:** Four 12-oz screw-cap jars were filled with the feed blend, prepared as described in I.A.3. above, and sealed. Single jars were stored in the dark at −20°, 5°, 25°, or 45° C for the 2-week stability study.

2. **Analysis procedure:** The analysis procedure used for the stability samples was the same as the method described in I.A.3. above with the exception of 5% hydrochloric acid in methanol (v/v) which was used to extract the samples in place of methanol alone.

3. **Quality assurance measures:** Sample analyses were performed with single color developments on three to six separate extracts. Because the feed blank absorbance was less than 0.002 AU, no correction was applied to the sample readings (approximately 0.400 AU). The analysis results were corrected for a mean zero-time spiked recovery yield of 86.8% ± 0.8% determined in triplicate. (This value is different from the previously given recovery because acidified extractant was used on these samples.) The spectrophotometer was calibrated with standard solutions of boric acid in methanol at concentrations of 0, 5, 10, and 15 µg/ml. The linear correlation coefficient calculated from the spectrophotometric data was 0.99999.

4. **Results**

| Storage Temperature | Boric Acid Found (ppm) (a,b) |
|---|---|
| −20° C | 965 ± 21 |
| 5° C | 952 ± 16 |
| 25° C | 885 ± 30 |
| 45° C | 893 ± 16 |

(a) Results were corrected for a mean zero-time spiked recovery yield of 86.8% ± 0.8%. The error values are maximum deviations of an assay value from the mean.
(b) The target concentration of boric acid was 1,000 ppm.

5. **Discussion:** The analysis for boric acid in feed was complicated by several factors. Boric acid readily forms complexes with proteins, free amino acids, and ammoniacal nitrogen in feed components. Initial attempts to extract and titrate boric acid with standard alkali as a complex with glycerol or mannitol failed because the feed complexes rendered the boric acid untitratable. Spikes of boric acid added to blank feed extract could not be determined by this method.

   The use of atomic absorption spectrophotometry for a dose analysis method was also unsuccessful because poor sensitivity for boron and high background from minerals in the feed combined to give very unreliable results at the low concentrations being tested.

   Of the other analysis methods considered, the modified curcumin method described in this report (Ogawa et al., 1979) exhibited high specificity for borate with excellent sensitivity (1 ppm) and did not require elaborate procedure or equipment.

The dose analysis method with methanol alone as the extractant (I.A.3.) was initially applied to the analysis of the stability of the samples. After samples were stored for 2 weeks at −20°, 5°, 25°, or 45° C, recoveries of boric acid of 93.6%, 81.7%, 52.3%, and 29.6%, respectively, were obtained. Further studies with the 2-week 45° C sample showed that boric acid recovery was directly related to the polarity of the extracting solvent. The 29.6% recovery with methanol alone increased to 77.4% when 1% hydrochloric acid in methanol was used. A further increase in recovery to 86.8% occurred when the hydrochloric acid concentration in the methanol was increased to 5%.

On zero-time spiked feeds, the difference in recovery between methanol alone and 5% hydrochloric acid in methanol was small (84.9% vs. 86.8%). Overall, these results illustrate the strong binding-complexing phenomenon experienced when boric acid is mixed with feed.

6. **Conclusions:** The recovery of boric acid from rodent feed stored 2 weeks at four temperatures was found to vary with the storage temperature and the polarity of the extracting solvent. Feed stored at −20° C or 5° C did not exhibit a statistically significant difference in recovery from the freshly blended homogeneity samples that were used for the stability study. The mean analysis values of the homogeneity samples, however, indicated approximately 2% loss during mixing, possibly due to complexing with feed components. The samples stored 2 weeks at 25° C or 45° C both exhibited approximately 8% loss relative to the −20° C samples. The experimental data seem to indicate that the chemical is stable but that it readily forms complexes with feed components which render it incompletely extractable by even strongly polar solvents (5% hydrochloric acid in methanol).

**C. Dose analysis method studies**

1. **Purpose:** Evaluation of an alternate colorimetric analysis method (Thorpe, 1978; Wolf, 1971) for boric acid in feed, employing azomethine H as the color reagent

2. **Special reagents and apparatus**

   a. **Azomethine H solution**--Dissolve 0.9 g azomethine H and 2.0 g ascorbic acid in 100 ml water; store in refrigerator and discard after 14 days.

   b. **Buffer-masking solution**--Dissolve 70 g of reagent-grade ammonium acetate, 5 g potassium acetate, 2 g nitrilotriacetic acid disodium salt, 5 g ethylenediaminetetraacetic acid, and 175 ml of 10% acetic acid (v/v) in 500 ml of water. This solution is stable.

   c. **Color developing reagent**--Dilute 14 ml of azomethine H solution (I.C.2.a.) and 30 ml of buffer-masking solution (I.C.2.b) to 100 ml with water and mix; prepare fresh daily.

   d. **Extracting solution**--methanol:water (1:1)

   e. **Micropipette**--Oxford or equivalent, equipped with plastic disposable tips, capable of accurately measuring repetitive 500-µl volumes

3. **Procedure:** The dilutions given in this method were calculated for samples ranging from 500 to 2,000 ppm boric acid in feed. For other concentrations, adjust sample weights and/or aliquot size as necessary to obtain sample absorbance readings between 0.3 and 0.75 AU.

   a. Accurately weigh and transfer 50-, 75-, 100-, 150-, and 200-mg quantities of boric acid to individual 50-ml volumetric flasks, dissolve in a few milliliters of extracting solution (I.C.2.d. above), dilute to 50 ml, and mix well.

   b. Pipette 5 ml of each standard solution into individual 200-ml centrifuge bottles containing 10 g of undosed feed and mix briefly. (These aliquots provide mixtures containing 500, 750, 1,000, 1,500, and 2,000 ppm boric acid.) Add 95 ml of extracting solution (I.C.2.d. above), and seal the bottles.

   c. Weigh triplicate 10-g portions of undosed feed for use as blanks, and weigh duplicate 10-g samples of dosed feed. Add 100 ml of extracting solution to the samples and the blanks and seal.

   d. Shake the standards, blanks, and formulated diet samples for 15 minutes on a mechanical shaker; centrifuge 5 minutes at approximately 1,800 rpm to clarify the extracts.

   e. With a micropipetter, transfer 500 µl of each extract to a 10-ml septum vial, and mix with 10 ml of azomethine H-color developing reagent (I.C.2.c. above). After sealing the vials and mixing, allow the solutions to react 1 hour at room temperature.

   f. Filter about 5 ml of each solution through a 0.5-µ Millipore filter and read the absorbance of the solutions in 1-cm cells at 420 nm versus water.

   g. Plot the net absorbance of each standard versus the milligrams of boric acid added per gram of feed and draw the best fitting line through the data points, or compute the linear regression equation from the same standard curve data to obtain the milligram per gram concentration of boric acid in the formulated diet sample.

4. **Azomethine H method evaluation studies**

   a. **Absorbance spectrum:** An absorbance spectrum was run on a reagent blank and on a boric acid standard. The spectra were scanned between 530 and 380 nm. From the spectra, it was evident that the azomethine H complex with boron does not exhibit a discrete absorption maximum but only shows a slight shoulder in the vicinity of 420 nm as it continues toward the ultraviolet region. The greatest difference in absorbance between the boron complex and the reagent blanks occurs at approximately 420 nm, and this wavelength was chosen for the determination.

b. **Effect of feed blank on color development:** For this study, four 10-g weight samples of undosed feed were extracted and treated as described in the dose method, I.C.3.c.-f. above. The absorbance readings obtained are shown below.

| | |
|---|---|
| Color reagent blank (no feed) | 0.145 |
| Color reagent + feed blank No. 1 | 0.148 |
| Color reagent + feed blank No. 2 | 0.152 |
| Color reagent + feed blank No. 3 | 0.155 |
| Color reagent + feed blank No. 4 | 0.153 |
| Mean feed blank | 0.152 ± 0.004 |
| Net contribution from feed | 0.007 ± 0.004 |

c. **Linearity of colorimetric measurement with different concentrations of boric acid:** Five 10-g portions of feed were spiked by carefully weighing and mixing graded levels of boric acid with the feed in 200-ml centrifuge bottles and processing the samples as described for the dose analysis method (I.C.3.). The following results were obtained.

| Sample | Boric Acid (ppm) | Absorbance at 420 nm | Net Absorbance (corrected for feed blank) |
|---|---|---|---|
| A | 504 | 0.257 | 0.105 |
| B | 749 | 0.324 | 0.172 |
| C | 1,001 | 0.400 | 0.248 |
| D | 1,502 | 0.560 | 0.408 |
| E | 2,003 | 0.705 | 0.553 |

The linear correlation coefficient calculated from the above data was 0.9998 with an intercept of −0.051. These results indicate a good conformity to Beer's law as well as uniform recovery of chemical over a fourfold range in concentration.

d. **Recovery of boric acid from feed:** In addition to the study in I.C.4.c. above, separately spiked food samples were analyzed and compared with neat standards. Results are shown below.

| Boric Acid Added (ppm) | Boric Acid Found (ppm) | Percent Recovery |
|---|---|---|
| 1,020 | 1,012 | 99.2 |
| 1,110 | 1,103 | 99.4 |

e. **Discussion:** The azomethine analysis method was definitely simpler and faster than the curcumin method, requiring only approximately 2 hours to complete an analysis. Conducting the analysis requires only a simple mixing of sample extract with color reagent; the sensitivity is quite adequate for the concentrations of the samples. With only slight modification of sample weight and/or aliquot size used for the color development, concentrations as low as 100 ppm can be easily determined.

f. **Conclusions:** An alternate method for analysis of boric acid in animal feed employing azomethine H as the color-developing reagent was evaluated for its applicability to dose analysis. The alternate method was simpler and faster (approximately 2 hours overall for analysis) and showed excellent recovery with linear response to dose level. The azomethine method was recommended as a replacement for the curcumin method originally proposed.

## II. Analysis of Formulated Diets for Mixing Homogeneity Conducted at the Study Laboratory

**A. Sampling and analysis:** Duplicate 2-g samples were taken from the top right, top left, and bottom portions of the blender for each of the 1,200- and 20,000-ppm dose mixtures. Samples were extracted and analyzed as described in Appendix F, Section I.

**B. Results**

| Sample Location | Target Concentration (ppm) | Determined Concentration (ppm) (a) | Percent of Target |
|---|---|---|---|
| Top left | 1,200 | 1,100 | 91.7 |
| Top right | 1,200 | 1,300 | 108.3 |
| Bottom | 1,200 | 1,100 | 91.7 |
| Top left | 20,000 | 19,600 | 98.0 |
| Top right | 20,000 | 20,000 | 100.0 |
| Bottom | 20,000 | 20,300 | 101.5 |

(a) Results of duplicate analysis

**C. Conclusions:** Concentrations were all within ±10% of the target values.

# APPENDIX F

# METHODS OF ANALYSIS OF FORMULATED DIETS

# APPENDIX F. METHODS OF ANALYSIS

## I. Study Laboratory

Duplicate samples of 2 g each were extracted with 50 ml of 50% aqueous methanol in 100-ml ground glass-stoppered graduated cylinders. Approximately 0.5 ml of each extract was clarified by centrifugation for 10 minutes at ≈2,000 rpm before 0.2-ml aliquots were transferred to 12-ml tubes with Teflon®-lined screw caps. To each tube was added 10 ml of azomethine color-developing solution that was prepared in advance as follows: 252 mg of azomethine H dissolved in 28 ml of 2% aqueous ascorbic acid and a masking buffer solution composed of 50 g of ammonium acetate, 3 g of disodium ethylenediaminetetraacetic acid, 80 ml of water, and 25 ml of glacial acetic acid were mixed and diluted to 200 ml with water. The reaction tubes were mixed and allowed to react for 40 minutes. The absorbances were read in 1-cm cells at 420 nm versus water in a Hitachi Model 100-40 spectrophotometer. Blanks and spiked feed samples were prepared and analyzed simultaneously.

## II. Analytical Chemistry Laboratory

Immediately before they were sampled for analysis, the referee feed sample and the undosed feed were equilibrated to room temperature and transferred to individual large-mouth glass jars. The samples were mixed by rotating for 20 minutes on a tumbler apparatus, with manual end-over-end tumbling every 5 minutes.

### A. Special reagents

1. **Azomethine H solution**--Dissolve 0.45 g azomethine H and 1.0 g ascorbic acid in 50 ml water. Store in refrigerator and discard after 14 days.

2. **Buffer-masking solution**--Dissolve 70 g of reagent-grade ammonium acetate, 5 g potassium acetate, 2 g nitrilotriacetic acid disodium salt, 5 g ethylenediaminetetraacetic acid, and 175 ml of 10% acetic acid (v/v) in 500 ml of water. This solution is stable.

3. **Color-developing reagent**--Dilute 35 ml of azomethine H solution and 75 ml of buffer-masking solution to 250 ml with water and mix. Prepare fresh daily.

4. **Extracting solution**--Methanol:water (1:1)

**B. Preparation of spiked feed standards:** Two standard solutions of boric acid were prepared independently in extracting solution. These solutions were diluted with extracting solution to make four additional standards. Aliquots (10 or 20 ml) of the six standard solutions were pipetted into individual 200-ml centrifuge bottles containing 5 g of undosed feed to make spiked feed standards bracketing the specified concentration range of the referee sample. One 200-ml centrifuge bottle containing 5 g of undosed feed was treated with 10 or 20 ml of extracting solution for use as a blank. The spiked feed standards and the feed blank were sealed and allowed to stand overnight at room temperature before they were used in the analysis procedure decribed below.

**C. Preparation of the referee sample:** Triplicate referee feed samples (approximately 5 g weighed to the nearest 0.001 g) were transferred to individual 200-ml centrifuge bottles. Extracting solution (10 or 20 ml) was pipetted into each sample, and then the bottles were sealed and allowed to stand overnight at room temperature before they were analyzed by the procedure described below.

D. **Analysis procedure:** Spiked feed standards, feed blank, and referee samples prepared as described above were each treated with extracting solution and shaken for 15 minutes at maximum stroke on a wrist-action shaker. The extracts were clarified by centrifugation for 5 minutes; then aliquots were mixed with azomethine color-developing reagent in septum vials. The vials were sealed with Teflon®-lined septa and allowed to react for 1 hour at room temperature. A 5-ml volume of each reacted solution was filtered through a 0.5-μ Millipore filter; then the absorbance of the solutions was measured versus deionized water in 1-cm quartz cells on a Cary 118 or Cary 219 spectrophotometer at 410 or 420 nm.

The amount of boric acid in the referee feed samples was determined from the linear regression equation obtained from the standard data, relating the absorbance of each spiked feed standard and blank sample to the amount of chemical in the respective spiked feed standard.

E. **Quality assurance measures:** The referee feed sample was analyzed in triplicate and the undosed feed sample was analyzed once or twice. Individually spiked portions of undosed feed (six concentrations bracketing the specified concentration range of the referee sample) were prepared from two independently weighed standards and were treated like the referee feed samples for obtaining standard data.

# APPENDIX G

# RESULTS OF ANALYSIS OF FORMULATED DIETS

TABLE G1. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF BORIC ACID

| Date Mixed | Target Concentration (ppm) | Determined Concentration (a) (ppm) | Percent of Target |
|---|---|---|---|
| 03/12/80 | 1,200 | 1,100 | 92 |
| 03/12/80 | 20,000 | 20,300 | 101 |
| 04/30/80 | 2,500 | 2,450 | 99 |
| 04/30/80 | 5,000 | 4,555 | 91 |
| 04/30/80 | 10,000 | 9,300 | 93 |

(a) Results of duplicate analysis

TABLE G2. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF BORIC ACID

| Date Mixed | Concentration of Boric Acid in Feed for Target Concentration (ppm) (a) 2,500 | 5,000 |
|---|---|---|
| 03/24/81 | 2,380 | 5,130 |
| 04/14/81 | 2,730 | 5,160 |
| 06/03/81 | 2,450 | 5,210 |
| 09/02/81 | 2,580 | 5,140 |
| 09/16/81 | 2,600 | 4,900 |
| 12/30/81 | 2,400 | 5,100 |
| 02/24/82 | 2,550 | 4,900 |
| 03/17/82 | 2,450 | 5,030 |
| 04/28/82 | 2,370 | 5,050 |
| 07/28/82 | 2,640 | 5,020 |
| 10/06/82 | 2,510 | 5,150 |
| 11/22/82 | 2,560 | 4,800 |
| 12/15/82 | 2,480 | 5,100 |
| 03/02/83 | 2,600 | 4,780 |
| Mean (ppm) | 2,521 | 5,034 |
| Standard deviation | 106 | 137 |
| Coefficient of variation (percent) | 4.2 | 2.7 |
| Range (ppm) | 2,370-2,730 | 4,780-5,210 |
| Number of samples | 14 | 14 |

(a) Results of duplicate analysis

TABLE G3. RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR FEED STUDIES OF BORIC ACID

| Date Mixed | Target Concentration (ppm) | Determined Concentration (ppm) Study Laboratory (a) | Referee Laboratory (b) |
|---|---|---|---|
| 03/24/81 | 2,500 | 2,380 | 2,540 |
| 09/02/81 | 5,000 | 5,140 | 4,660 |
| 02/24/82 | 2,500 | 2,550 | 2,640 |
| 10/06/82 | 5,000 | 5,150 | 5,390 |
| 03/02/83 | 2,500 | 2,600 | 2,450 |

(a) Results of duplicate analysis
(b) Results of triplicate analysis

# APPENDIX H

# SENTINEL ANIMAL PROGRAM

# APPENDIX H. SENTINEL ANIMAL PROGRAM

## I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen $B6C3F_1$ mice are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

| Hemagglutination Inhibition | Complement Fixation | ELISA |
|---|---|---|
| PVM (pneumonia virus of mice) | M.Ad. (mouse adenovirus) | MHV (mouse hepatitis virus) |
| Reo 3 (reovirus type 3) | LCM (lymphocytic choriomeningitis virus) | |
| GDVII (Theiler's encephalomyelitis virus) | | |
| Poly (polyoma virus) | | |
| MVM (minute virus of mice) | | |
| Ectro (infectious ectromelia) | | |
| Sendai | | |

## II. Results

TABLE H1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR MICE IN THE TWO-YEAR FEED STUDIES OF BORIC ACID (a)

| Interval (months) | No. of Animals | Positive Serologic Reaction for |
|---|---|---|
| 6 | -- | None positive |
| 12 | -- | None positive |
| 18 | -- | None positive |
| 24 | 6/10 | MHV |

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for the Animal Disease Screening Program.

# APPENDIX I

# FEED AND COMPOUND CONSUMPTION BY MICE IN THE TWO-YEAR FEED STUDIES OF BORIC ACID

TABLE I1. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID

| | Control | | Low Dose | | | | High Dose | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | Grams Feed/ Day (a) | Body Weight (grams) | Grams Feed/ Day (a) | Body Weight (grams) | Low/ Control (b) | Dose/ Day (c) | Grams Feed/ Day (a) | Body Weight (grams) | High/ Control (b) | Dose/ Day (c) |
| 4 | 5 | 26.7 | 5 | 27.7 | 1.0 | 451 | 6 | 27.6 | 1.2 | 1,087 |
| 8 | 6 | 29.7 | 6 | 30.5 | 1.0 | 492 | 6 | 30.1 | 1.0 | 997 |
| 16 | 5 | 33.1 | 6 | 32.9 | 1.2 | 456 | 6 | 32.5 | 1.2 | 923 |
| 20 | 3 | 33.9 | 4 | 33.0 | 1.3 | 303 | 4 | 30.3 | 1.3 | 660 |
| 24 | 3 | 35.6 | 4 | 34.2 | 1.3 | 292 | 5 | 30.6 | 1.7 | 817 |
| 28 | 6 | 37.9 | 7 | 38.1 | 1.2 | 459 | 8 | 34.8 | 1.3 | 1,149 |
| 32 | 5 | 38.8 | 6 | 39.0 | 1.2 | 385 | 6 | 35.0 | 1.2 | 857 |
| 36 | 5 | 39.8 | 6 | 39.8 | 1.2 | 377 | 7 | 35.3 | 1.4 | 992 |
| 40 | 5 | 41.1 | 5 | 40.8 | 1.0 | 306 | 6 | 35.4 | 1.2 | 847 |
| 44 | 6 | 41.1 | 7 | 40.8 | 1.2 | 429 | 9 | 35.7 | 1.5 | 1,261 |
| 48 | 6 | 41.0 | 6 | 42.1 | 1.0 | 356 | 8 | 36.9 | 1.3 | 1,084 |
| 52 | 5 | 43.4 | 5 | 42.5 | 1.0 | 294 | 8 | 38.3 | 1.6 | 1,044 |
| 56 | 5 | 43.9 | 6 | 41.9 | 1.2 | 358 | 9 | 37.6 | 1.8 | 1,197 |
| 60 | 5 | 44.1 | 6 | 42.5 | 1.2 | 353 | 9 | 37.6 | 1.8 | 1,197 |
| 64 | 5 | 43.3 | 6 | 41.5 | 1.2 | 361 | 9 | 37.4 | 1.8 | 1,203 |
| 68 | 6 | 43.7 | 6 | 41.2 | 1.0 | 364 | 9 | 36.7 | 1.5 | 1,226 |
| 72 | 5 | 43.4 | 6 | 40.9 | 1.2 | 367 | 9 | 36.3 | 1.8 | 1,240 |
| 76 | 3 | 42.8 | 4 | 39.9 | 1.3 | 251 | 6 | 37.1 | 2.0 | 809 |
| 80 | 6 | 43.1 | 7 | 39.3 | 1.2 | 445 | 11 | 37.4 | 1.8 | 1,471 |
| 89 | 3 | 42.0 | 4 | 40.7 | 1.3 | 246 | 5 | 37.3 | 1.7 | 670 |
| 92 | 4 | 42.6 | 7 | 39.9 | 1.8 | 439 | 10 | 37.3 | 2.5 | 1,340 |
| 96 | 5 | 42.3 | 7 | 37.4 | 1.4 | 468 | 11 | 35.2 | 2.2 | 1,563 |
| 100 | 5 | 41.7 | 7 | 39.5 | 1.4 | 443 | 12 | 36.5 | 2.4 | 1,644 |
| Mean | 4.9 | 39.8 | 5.8 | 38.5 | 1.2 | 378 | 7.8 | 35.2 | 1.6 | 1,099 |
| SD (d) | 1.0 | | 1.0 | | 0.2 | 72 | 2.2 | | 0.4 | 263 |
| CV (e) | 20.4 | | 17.2 | | 16.7 | 19.0 | 28.2 | | 25.0 | 23.9 |

(a) Grams of feed removed from feed per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Milligrams of boric acid consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE I2. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF BORIC ACID

| | Control | | Low Dose | | | | High Dose | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | Grams Feed/ Day (a) | Body Weight (grams) | Grams Feed/ Day (a) | Body Weight (grams) | Low/ Control (b) | Dose/ Day (c) | Grams Feed/ Day (a) | Body Weight (grams) | High/ Control (b) | Dose/ Day (c) |
| 4 | 5 | 21.6 | 5 | 21.7 | 1.0 | 576 | 6 | 21.3 | 1.2 | 1,408 |
| 8 | 6 | 23.7 | 6 | 24.0 | 1.0 | 625 | 6 | 23.7 | 1.0 | 1,266 |
| 16 | 5 | 27.0 | 5 | 26.4 | 1.0 | 473 | 7 | 25.9 | 1.4 | 1,351 |
| 20 | 4 | 28.0 | 4 | 27.0 | 1.0 | 370 | 4 | 25.8 | 1.0 | 775 |
| 24 | 4 | 29.7 | 4 | 28.3 | 1.0 | 353 | 4 | 26.1 | 1.0 | 766 |
| 28 | 7 | 31.7 | 7 | 30.3 | 1.0 | 578 | 8 | 28.5 | 1.1 | 1,404 |
| 32 | 6 | 33.2 | 7 | 30.8 | 1.2 | 568 | 7 | 29.6 | 1.2 | 1,182 |
| 36 | 5 | 33.1 | 6 | 31.8 | 1.2 | 472 | 7 | 29.9 | 1.4 | 1,171 |
| 40 | 5 | 35.6 | 5 | 33.3 | 1.0 | 375 | 6 | 30.3 | 1.2 | 990 |
| 44 | 6 | 36.1 | 8 | 33.3 | 1.3 | 601 | 9 | 31.2 | 1.5 | 1,442 |
| 48 | 6 | 35.2 | 7 | 34.1 | 1.2 | 513 | 8 | 32.3 | 1.3 | 1,238 |
| 52 | 6 | 38.9 | 6 | 36.3 | 1.0 | 413 | 8 | 33.7 | 1.3 | 1,187 |
| 56 | 6 | 39.4 | 7 | 36.8 | 1.2 | 476 | 10 | 33.9 | 1.7 | 1,475 |
| 60 | 6 | 40.9 | 7 | 37.8 | 1.2 | 463 | 8 | 34.6 | 1.3 | 1,156 |
| 64 | 6 | 39.6 | 7 | 37.7 | 1.2 | 464 | 9 | 34.8 | 1.5 | 1,293 |
| 68 | 7 | 40.2 | 8 | 37.5 | 1.1 | 533 | 9 | 34.4 | 1.3 | 1,308 |
| 72 | 7 | 40.6 | 7 | 38.4 | 1.0 | 456 | 9 | 33.8 | 1.3 | 1,331 |
| 76 | 4 | 40.7 | 5 | 38.4 | 1.3 | 326 | 6 | 34.4 | 1.5 | 872 |
| 80 | 7 | 39.7 | 9 | 38.0 | 1.3 | 592 | 10 | 33.5 | 1.4 | 1,493 |
| 89 | 4 | 42.8 | 5 | 39.7 | 1.3 | 315 | 6 | 35.2 | 1.5 | 852 |
| 92 | 5 | 41.6 | 8 | 40.1 | 1.6 | 499 | 9 | 35.4 | 1.8 | 1,271 |
| 96 | 6 | 41.9 | 9 | 40.1 | 1.5 | 561 | 10 | 35.3 | 1.7 | 1,416 |
| 100 | 6 | 43.7 | 9 | 40.4 | 1.5 | 557 | 9 | 37.1 | 1.5 | 1,213 |
| Mean | 5.6 | 35.9 | 6.6 | 34.0 | 1.2 | 485 | 7.6 | 31.3 | 1.4 | 1,211 |
| SD (d) | 1.0 | | 1.5 | | 0.2 | 92 | 1.8 | | 0.2 | 220 |
| CV (e) | 17.9 | | 22.7 | | 16.7 | 19.0 | 23.7 | | 14.3 | 18.2 |

(a) Grams of feed removed from feed per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Milligrams of boric acid consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

# APPENDIX J

# INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

## Meal Diet: April 1981 to April 1983

**(Manufactured by Zeigler Bros., Inc., Gardners, PA)**

TABLE J1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

| Ingredients (b) | Percent by Weight |
|---|---|
| Ground #2 yellow shelled corn | 24.50 |
| Ground hard winter wheat | 23.00 |
| Soybean meal (49% protein) | 12.00 |
| Fish meal (60% protein) | 10.00 |
| Wheat middlings | 10.00 |
| Dried skim milk | 5.00 |
| Alfalfa meal (dehydrated, 17% protein) | 4.00 |
| Corn gluten meal (60% protein) | 3.00 |
| Soy oil | 2.50 |
| Brewer's dried yeast | 2.00 |
| Dry molasses | 1.50 |
| Dicalcium phosphate | 1.25 |
| Ground limestone | 0.50 |
| Salt | 0.50 |
| Premixes (vitamin and mineral) | 0.25 |

(a) NIH, 1978; NCI, 1976
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE J2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

| | Amount | Source |
|---|---|---|
| **Vitamins** | | |
| A | 5,500,000 IU | Stabilized vitamin A palmitate or acetate |
| $D_3$ | 4,600,000 IU | D-activated animal sterol |
| $K_3$ | 2.8 g | Menadione activity |
| *d*-α-Tocopheryl acetate | 20,000 IU | |
| Choline | 560.0 g | Choline chloride |
| Folic acid | 2.2 g | |
| Niacin | 30.0 g | |
| *d*-Pantothenic acid | 18.0 g | *d*-Calcium pantothenate |
| Riboflavin | 3.4 g | |
| Thiamine | 10.0 g | Thiamine mononitrate |
| $B_{12}$ | 4,000 µg | |
| Pyridoxine | 1.7 g | Pyridoxine hydrochloride |
| Biotin | 140.0 mg | *d*-Biotin |
| **Minerals** | | |
| Iron | 120.0 g | Iron sulfate |
| Manganese | 60.0 g | Manganous oxide |
| Zinc | 16.0 g | Zinc oxide |
| Copper | 4.0 g | Copper sulfate |
| Iodine | 1.4 g | Calcium iodate |
| Cobalt | 0.4 g | Cobalt carbonate |

(a) Per ton (2,000 lb) of finished product

TABLE J3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

| Nutrient | Mean ± Standard Deviation | Range | Number of Samples |
|---|---|---|---|
| Crude protein (percent by weight) | 24.19 ± 1.07 | 22.4-26.3 | 25 |
| Crude fat (percent by weight) | 5.02 ± 0.47 | 4.2-6.0 | 25 |
| Crude fiber (percent by weight) | 3.37 ± 0.37 | 2.4-4.2 | 25 |
| Ash (percent by weight) | 6.54 ± 0.26 | 5.97-7.03 | 25 |
| **Essential Amino Acids (percent of total diet)** | | | |
| Arginine | 1.300 | 1.21-1.38 | 3 |
| Cystine | 0.340 | 0.23-0.40 | 3 |
| Glycine | 1.137 | 1.06-1.20 | 3 |
| Histidine | 0.561 | 0.530-0.578 | 3 |
| Isoleucine | 0.899 | 0.881-0.934 | 3 |
| Leucine | 1.930 | 1.85-1.98 | 3 |
| Lysine | 1.243 | 1.20-1.30 | 3 |
| Methionine | 0.329 | 0.306-0.368 | 3 |
| Phenylalanine | 0.991 | 0.960-1.04 | 3 |
| Threonine | 0.851 | 0.827-0.886 | 3 |
| Tryptophan | 0.187 | 0.171-0.211 | 3 |
| Tyrosine | 0.647 | 0.566-0.769 | 3 |
| Valine | 1.090 | 1.05-1.12 | 3 |
| **Essential Fatty Acids (percent of total diet)** | | | |
| Linoleic | 2.40 | 2.37-2.44 | 2 |
| Linolenic | 0.284 | 0.259-0.308 | 2 |
| **Vitamins** | | | |
| Vitamin A (IU/kg) | 11,936 ± 2,547 | 8,900-22,000 | 25 |
| Vitamin D (IU/kg) | 5,220 | 4,140-6,300 | 2 |
| α-Tocopherol (ppm) | 39.1 | 31.1-44.0 | 3 |
| Thiamine (ppm) | 18.7 ± 3.20 | 14.0-26.0 | (b) 24 |
| Riboflavin (ppm) | 7.3 | 6.1-8.1 | 3 |
| Niacin (ppm) | 82 | 65-97 | 3 |
| Pantothenic acid (ppm) | 30.2 | 23.0-30.5 | 3 |
| Pyridoxine (ppm) | 7.7 | 5.6-8.8 | 3 |
| Folic acid (ppm) | 2.5 | 1.8-3.4 | 3 |
| Biotin (ppm) | 0.27 | 0.21-0.32 | 3 |
| Vitamin $B_{12}$ (ppb) | 21.2 | 10.6-38.0 | 3 |
| Choline (ppm) | 3,337 | 3,200-3,430 | 3 |
| **Minerals** | | | |
| Calcium (percent) | 1.22 ± 0.10 | 1.10-1.45 | 25 |
| Phosphorus (percent) | 0.96 ± 0.05 | 0.84-1.10 | 25 |
| Potassium (percent) | 0.809 | 0.772-0.846 | 2 |
| Chloride (percent) | 0.581 | 0.479-0.635 | 3 |
| Sodium (percent) | 0.307 | 0.258-0.349 | 3 |
| Magnesium (percent) | 0.165 | 0.151-0.177 | 3 |
| Sulfur (percent) | 0.292 | 0.270-0.290 | 3 |
| Iron (ppm) | 420 | 409-431 | 3 |
| Manganese (ppm) | 87.7 | 81.7-95.5 | 3 |
| Zinc (ppm) | 52.1 | 46.1-56.0 | 3 |
| Copper (ppm) | 11.15 | 8.09-15.70 | 3 |
| Iodine (ppm) | 2.66 | 1.52-3.64 | 3 |
| Chromium (ppm) | 1.72 | 1.44-1.93 | 3 |
| Cobalt (ppm) | 0.64 | 0.49-0.78 | 3 |

(a) Two or three batches of feed analyzed for nutrients reported in this table were manufactured in 1983 and 1984.
(b) One batch (7/22/81) was not analyzed for thiamine.

TABLE J4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

| Contaminant | Mean ± Standard Deviation | Range | Number of Samples |
|---|---|---|---|
| Arsenic (ppm) | 0.45 ± 0.11 | 0.21-0.65 | 25 |
| Cadmium (ppm) (a) | <0.1 | | 25 |
| Lead (ppm) | 0.95 ± 0.78 | 0.27-2.93 | 25 |
| Mercury (ppm) (a) | < 0.05 25 | | |
| Selenium (ppm) | 0.28 ± 0.06 | 0.16-0.40 | 25 |
| Aflatoxins (ppb) (a,b) | <10 | <5.0-10.0 | 25 |
| Nitrate nitrogen (ppm) (c) | 9.85 ± 4.55 | 0.6-19.0 | 25 |
| Nitrite nitrogen (ppm) (c) | 1.92 ± 1.28 | 0.4-5.3 | 25 |
| BHA (ppm) (d) | 5.67 ± 5.07 | 1.5-20.0 | 25 |
| BHT (ppm) (d) | 3.35 ± 2.55 | <1.0-13.0 | 25 |
| Aerobic plate count (CFU/g) | 121,420 ± 94,844 | 7,000-420,000 | 25 |
| Coliform (MPN/g) (e) | 965 ± 991 | <3-2,400 | 25 |
| *E. coli* (MPN/g) (e,f) | 6.76 ± 7.06 | <3-23 | 24 |
| *E. coli* (MPN/g) (e,g) | 12.64 ± 29.46 | <3-150 | 25 |
| Total nitrosamines (ppb) (h,i) | 4.40 ± 3.16 | <1.2-12.9 | 24 |
| Total nitrosamines (ppb) (h,j) | 8.29 ± 19.41 | 1.2-100.3 | 25 |
| *N*-Nitrosodimethylamine (ppb) (h,k) | 3.05 ± 3.05 | 0.6-12.0 | 24 |
| *N*-Nitrosodimethylamine (ppb) (h,l) | 6.89 ± 19.42 | 0.6-99.0 | 25 |
| *N*-Nitrosopyrrolidine (ppb) | 1.20 ± 0.62 | <0.3-2.4 | 25 |
| **Pesticides (ppm)** | | | |
| α-BHC (a,m) | <0.01 | | 25 |
| β-BHC (a) | <0.02 | | 25 |
| γ-BHC-Lindane (a) | <0.01 | | 25 |
| δ-BHC (a) | <0.01 | | 25 |
| Heptachlor (a) | <0.01 | | 25 |
| Aldrin (a) | <0.01 | | 25 |
| Heptachlor epoxide (a) | <0.01 | | 25 |
| DDE (a,n) | <0.01 | 0.05 (7/14/81) | 25 |
| DDD (a) | <0.01 | | 25 |
| DDT (a) | <0.01 | | 25 |
| HCB (a) | <0.01 | | 25 |
| Mirex (a) | <0.01 | | 25 |
| Methoxychlor (a,o) | <0.05 | 0.13 (8/25/81); 0.6 (6/29/82) | 25 |
| Dieldrin (a) | <0.01 | | 25 |
| Endrin (a) | <0.01 | | 25 |
| Telodrin (a) | <0.01 | | 25 |
| Chlordane (a) | <0.05 | | 25 |
| Toxaphene (a) | <0.1 | | 25 |
| Estimated PCBs (a) | <0.2 | | 25 |
| Ronnel (a) | <0.01 | | 25 |
| Ethion (a) | <0.02 | | 25 |
| Trithion (a) | <0.05 | | 25 |
| Diazinon (a) | <0.1 | | 25 |
| Methyl parathion (a) | <0.02 | | 25 |
| Ethyl parathion (a) | <0.02 | | 25 |
| Malathion (p) | 0.08 ± 0.05 | <0.05-0.25 | 25 |
| Endosulfan I (a) | <0.01 | | 25 |
| Endosulfan II (a) | <0.01 | | 25 |
| Endosulfan sulfate (a) | <0.03 | | 25 |

TABLE J4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) MPN = most probable number
(f) Mean, standard deviation, and range exclude one value of 150 for the batch produced on 8/26/82.
(g) Mean, standard deviation, and range include the high value given in footnote f.
(h) All values were corrected for percent recovery.
(i) Mean, standard deviation, and range exclude one value of 100.3 ppb for the batch produced on 4/27/81.
(j) Mean, standard deviation, and range include the high value given in footnote i.
(k) Mean, standard deviation, and range exclude one value of 99.0 for the batch produced on 4/27/81.
(l) Mean, standard deviation, and range include the high value listed in footnote k.
(m) BHC = hexachlorocyclohexane or benzene hexachloride
(n) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(o) Two observations were above the detection limit. The value and the date they were obtained are listed under the range.
(p) Ten batches contained more than 0.05 ppm.

# APPENDIX K

# DATA AUDIT SUMMARY

# APPENDIX K. DATA AUDIT SUMMARY

The experimental data on the toxicology and carcinogenesis studies of boric acid were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The 2-year studies in mice were begun in March 1981 and completed in April 1983 at EG&G Mason Research Institute, Worcester, Massachusetts, under a subcontract with Tracor Jitco, Inc. The data audit was conducted by Dynamac Corporation under a contract for NTP. The individuals involved in the audit were J. Albert, M.S., J. Bhandari, D.V.M., Ph.D., R. Bowman, B.S., D. Copeland, D.V.M., D.A.C.V.P., J. Kovach, B.A., S. Shrivastava, Ph.D., and S. Taulbee.

The full report of NTP audit is on file at the National Toxicology Program, NIEHS. The audit included, but was not limited to, a review of the records of the inlife portion of the studies for 10% of the animals, 100% of the available chemistry data, and a random 50% sample of the chemical mix calculations. All Individual Animal Data Records were examined for correspondence between necropsy observations and histopathologic findings. All wet tissue bags were counted, and 10% were reviewed for animal identification and the presence of untrimmed lesions. A complete slide-block match for both sexes in the high dose and control groups was performed.

The audit for boric acid indicated that the inlife and chemistry portions were complete and adequate. The pathology audit of the residual wet tissues identified 11/63 carcasses with ear punch/notches that were either unreadable or torn. The audit identified 17 gross observations that had no microscopic diagnoses. Only one was a tumor, and none affected interpretation of the pathology data. Some untrimmed potential tumors were found during the audit of the wet tissues, but these were subsequently reviewed, trimmed, and examined microscopically.

In summary, the audit of data and specimens supports the results presented in this Technical Report.


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