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CARCINOGENESIS BIOASSAY OF L-ASCORBIC ACID (VITAMIN C) (CAS NO. 50-81-7) IN F344/N RATS AND B6C3F1 MICE (FEED STUDY)

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 chemically induced 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 comprised of four charter DHHS agencies: the National Cancer Institute, National Institutes of Health; the National Institute of Environmental Health Sciences, National Institutes of Health; the National Center for Toxicological Research, Food and Drug Administration; and the National Institute for Occupational Safety and Health, Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT
ON THE

CARCINOGENESIS BIOASSAY
OF
L-ASCORBIC ACID (VITAMIN C)

(CAS NO. 50-81-7)

IN F344/N RATS AND B6C3F1 MICE
(FEED STUDY)

NATIONAL TOXICOLOGY PROGRAM
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and
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NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis bioassay 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 is a potential 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.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room A-306, Landow Building, Bethesda, MD 20205 (301-496-1152) or at Research Triangle Park, NC 27709 (919-541-3991).

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), 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.

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 carcinogenesis bioassay 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.

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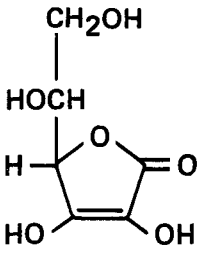
CARCINOGENESIS BIOASSAY OF L-ASCORBIC ACID (VITAMIN C)



L-ASCORBIC ACID

CAS NO. 50-81-7

ABSTRACT

A carcinogenesis bioassay of L-ascorbic acid (>97% pure) was conducted by administering diets containing 25,000 or 50,000 ppm L-ascorbic acid to groups of 50 F344/N rats and 50 B6C3F$_1$ mice of each sex for 103 weeks. Controls consisted of 50 untreated rats and untreated mice of each sex. Fifty-thousand ppm is the highest dose recommended for chronic studies.

Survival of dosed and control female rats and of dosed and control female mice were comparable. Survival of high-dose male rats was slightly greater than that of the controls (P=0.087). Survival of high-dose male mice was significantly greater (P=0.009) than that of the controls. Throughout most of the study, mean body weights of dosed female rats and dosed female mice were lower than those of the controls. Final body weights were comparable among groups, except for the high-dose female rats (<13%); marginal differences (<8%) were observed for low-dose female rats and for dosed female mice (8%-11%). Food consumption was equivalent among groups.

Most observational differences were confined to the female rat. The incidence of low-dose female rats with undifferentiated (mononuclear-cell) leukemias (control, 6/50, 12%; low-dose, 17/50, 34%; high-dose, 12/50, 24%) was significantly higher (P<0.02) than that in controls. These tumors were not considered to be related to administration of L-ascorbic acid because they did not occur in the female high-dose group at incidences significantly greater (P>0.07) than those in the controls, the trend test was not significant (P≥0.07), and no increases were observed for male rats.

Under the conditions of this bioassay, L-ascorbic acid was not carcinogenic for male and female F344/N rats or male and female B6C3F$_1$ mice.

CONTRIBUTORS

This bioassay of L-ascorbic acid was conducted at Battelle Columbus Laboratories under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The 2-year study of mice was begun in May 1978 and was completed in May 1980; the 2-year study in rats was begun in November 1978 and was terminated in November 1980.

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The chemicals used in this bioassay of L-ascorbic acid were analyzed by the Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri 64110; reanalysis of the bulk chemical and analysis of formulated diets were performed at Battelle Columbus Laboratories.

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*Unable to attend June 16, 1982 meeting

SUMMARY OF PEER REVIEW COMMENTS

On June 16, 1982 this carcinogenesis bioassay technical report on L-ascorbic acid (Vitamin C) underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. This public review meeting began at 9:00 a.m. in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The following precis represents the critiques made by the principal reviewers as well as comments from and discussion by the Peer Review Panel, NTP staff, and attendees.

Dr. Vore, a principal reviewer for the report on the bioassay of L-ascorbic acid, agreed with the conclusion that: "Under the conditions of this bioassay, L-ascorbic acid was not carcinogenic for F334/N rats or B6C3F$_1$ mice of either sex." She noted the high dose chosen, 50,000 ppm, is the highest concentration recommended for chronic feeding by the Program. She said no mention was made of the significant negative trend for pituitary adenomas in female rats. Also, the pairwise comparison for high dose vs. control was statistically significant. She said that negative trends for both neoplastic and nonneoplastic lesions should be highlighted in the report, although not necessarily included in the abstract. She raised the question as to the implications of highlighting such information. For such a popular over-the-counter preparation as ascorbic acid, she was pleased that the results of this bioassay were negative.

Dr. J. Douglas, NTP, responded to Dr. Vore's comment about pituitary adenomas in female rats. He said that when one combines adenomas and carcinomas of the pituitary gland (the most meaningful interpretative approach), the differential comparisons disappear in every instance except for the borderline (P=0.05) incidental tumor trend test.

As a second principal reviewer, Dr. Breslow agreed with the conclusion as stated. He criticized as misleading some of the phrasing used to describe the statistical significance of observed results. He expressed the opinion that rather routine and uncritical use was being made of historical control data in order to interpret marginally significant differences in incidence rates between control and dosed animals which appear in isolated species/sex/site combinations. Better understanding of factors responsible for inter-laboratory and within laboratory inter-experiment variation is desirable before one can confidently exclude all such results as being statistical aberrations. He noted the significant negative trends for a variety of nonneoplastic degenerative lesions were interesting and merited further investigation.

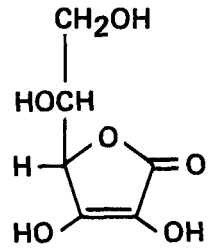
In response to Dr. Breslow's comments, Dr. J. Haseman, NTP, said three problems have kept NTP from fully utilizing historical control data. The first was defining the NTP historical data base; the second, identifying and quantifying the factors responsible for extra binomial variation frequently seen in tumor incidence; and the third, selecting appropriate statistical methodology to utilize the historical control data. He said that the first of these problems has recently been resolved and that progress is being made in resolving the other two issues. Dr. Haseman informed the Panel members that this important topic would be presented to the Board of Scientific Counselors in September 1982. [Minutes of that meeting are available upon request.] He expressed the hope that in the near future NTP would be able to make more appropriate and uniform use of the historical data base in a formal testing framework.

As a third principal reviewer, Dr. Swenberg agreed that the bioassay was well conducted and the report well written and documented. He noted several items that needed minor revision. He submitted an abstract of a report by a Japanese researcher showing that sodium L-ascorbate following a nitrosamine initiator can promote cancer of the urinary bladder in rats (Ito, 1981).

Dr. Swenberg moved that the report on the bioassay of L-ascorbic acid be accepted with the revisions discussed. Dr. Schwetz seconded the motion and the technical report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

I. INTRODUCTION



L-ASCORBIC ACID

CAS NO. 50-81-7

L-Ascorbic acid (vitamin C) is essential for many physiologic functions in animals and humans, mostly biochemical reactions involving oxidation (AMA, 1980). It is involved in the formation of collagen, probably including the conversion of proline to hydroxyproline (Murad et al., 1981). All mammals except humans, primates, and guinea pigs can synthesize L-ascorbic acid endogenously. Humans, for instance, lack the hepatic enzyme necessary to synthetically convert L-gulonolactone to L-ascorbic acid, the final step in the *in vivo* synthesis.

L-Ascorbic acid is approved for use as a dietary supplement and chemical preservative by the U.S. Food and Drug Administration and is on the FDA's list of substances generally recognized as safe (GRAS) (CFR, 1974).

L-Ascorbic acid may be used in soft drinks as an antioxidant for flavor ingredients, in meat and meat-containing products, for curing and pickling, in flour to improve baking quality, in beer as a stabilizer, in fats and oils as an antioxidant, and in a wide variety of foods for vitamin C enrichment (Merck, 1976; Klaui, 1974; Kirk-Othmer, 1963 and 1978). L-Ascorbic acid may also find use in stain removers, hair waving preparations, plastics manufacture, photography, and water treatment (Klaui, 1974).

Approximately 3,000 tons of L-ascorbic acid were produced in the United States in 1961 (Kirk-Othmer, 1963). Recent production figures are not available (USITC, 1981), but it would be expected that production has not diminished in the past few years.

Extensive literature has appeared on the use of ascorbic acid in treating a wide variety of diseases. It is claimed that megadose regimens can prevent or cure viral respiratory infections and the "common cold" (Pauling, 1970) and that they are beneficial in treating cancer (Cameron and Pauling, 1979). More clinical data must be collected; this is now being done.

A deficiency of L-ascorbic acid leads to degeneration of collagen and intercellular ground substances, the resulting effects of which are referred to as the scurvy syndrome (Gilman et al., 1980). This is usually prevented by intake of fresh fruits and vegetables containing L-ascorbic acid (e.g., cabbage, tomatoes, and citrus fruits), as well as other foods fortified with vitamin C (AMA, 1980; Kirk-Othmer, 1963 and 1978). The daily dietary allowance recommended by the National Research Council is 60 mg, an amount sufficient to accommodate the needs of an adult human (Calabrese, 1980; Gilman et al., 1980). Higher daily doses are recommended for pregnant or lactating women, and doses of 200-500 mg are sometimes administered to victims of severe burns due to the effects on connective tissue. Some persons have advocated intakes that are in excess of these reported tissue saturation levels (Pauling, 1970; Stone, 1974); these authors suggest doses of 3,000 mg per day.

Untoward effects that have been claimed to follow chronic high-dose intake of Vitamin C include the formation of kidney stones resulting from increased excretion of oxalate (Gilman et al., 1980). Since there is a dearth of clinical case reports on ascorbic acid toxicity in humans, either this chemical possesses remarkably little toxicity or humans have the ability to accommodate wide ranges of intake.

Human breast milk contains 30 to 50 mg of ascorbic acid per liter, depending on the mother's intake (Irwin and Hutchins, 1976; Gilman et al., 1980). Consequently, the infant consuming 850 ml of breast milk will receive about 35 mg of ascorbic acid, the RDA for infants.

Unstressed male Wistar rats (Curtin and King, 1955; Burns et al., 1954) and male Sprague-Dawley rats (Salomon and Stubbs, 1961) are reported to produce 20-58 mg/kg/day. Under stress, rats produce approximately 217 mg/kg day (Stone, 1974). Mice are reported to produce 275 mg/kg/day (Stone, 1974). If humans were to consume amounts similar to those produced by unstressed rats, a person weighing 60 kg would take in about 1,200 to 3,600 mg per day.

L-Ascorbic acid was found in the adrenal and pituitary glands of rats at concentrations of 280-400 mg/100 g tissue and 100-130 mg/100 g tissue, and in the adrenal and pituitary glands of adult humans at concentrations of 30-40 mg/100 g tissue and 40-50 mg/100 g tissue. Concentrations exceeding 10-15 mg/100 g tissue are found in the spleen, brain, liver, kidney, testes, eye lens, and white blood cells of both rats (strain unstated) and humans (Hornig, 1975). In another study, rats and mice of unspecified strains were found to have L-ascorbic acid concentrations of 508 and 808 mg/100 g tissue in the adrenal glands and 349 and 1,052 mg/100 g in the ovaries (Bhatavdekar and Shah, 1980). Concentrations of L-ascorbic acid in the pituitary gland were not reported. The body pool of ascorbic acid in rats (strain unspecified) has been calculated to be 10.7 mg/100 g body weight (Conney et al., 1961).

Ascorbic acid undergoes biochemical degradation in the body and, when excess is administered, can be excreted unchanged. The renal excretion threshold for vitamin C in humans is approximately 1.4 mg %. Ascorbic acid is oxidized to carbon dioxide in guinea pigs and rats and to oxalate in man (Burns et al., 1954; Gilman et al., 1980). When ^{14}C-ascorbic acid was administered by intraperitoneal injection to rats of an unspecified strain at doses of 44 or 51 mg, 0.57% or 1.18% of the dose was found as labelled oxalic acid in the urine (Takenouchi et al., 1966). L-Xylonic acid, L-lyxonic acid, ascorbic acid-2-sulfate, and 2-methyl-L-ascorbic acid have been identified as metabolites of L-ascorbic acid in rats (Mumma and Verlangieri, 1972; Hornig, 1975; Curtin and King, 1955; Blaschke and Hertting, 1971; Ashwell et al., 1961; Kanfer et al., 1960; Takenouchi et al., 1966; Tolbert et al., 1975). According to Tolbert et al. (1975), the metabolism of ascorbic acid depends on several factors, including (among other things) the route of administration, dosage, and the nutritional status of the animal.

The oral LD_{50} of L-ascorbic acid in rats is reported to be greater than 5,000 mg/kg body weight (Demole, 1934). The cause of death was not stated. Hypercholesterolemia, an increase in blood glucose, and a decrease in blood urea nitrogen, has been found in male and female Helwan farm rats 15 minutes and 1 hour after administration of 100 mg/kg ascorbic acid by intraperitoneal injection (El-Banna et al., 1978).

No compound-related toxic effects were observed when L-ascorbic acid was administered by gavage (100 mg/100 g body weight) for 6 weeks to male albino Charles Foster rats or incorporated into the diets of male and female rats for 2 years (strain unspecified), at a concentration equivalent to 200 mg/100 g body weight (Nandi et al., 1973; Surber and Cerioli, 1971). However, a dose-related decrease in body-weight and increases in relative thyroid and pituitary weights were found when male rats of unspecified strain were administered daily injections of 1, 10, or 100 mg L-ascorbic acid per 100 g body weight for 21 days (Marcusen and Heninger, 1976).

Ascorbic acid was not mutagenic in a dominant lethal test in Wistar rats (Chauhan et al., 1978). L-ascorbic acid has been found to induce DNA repair synthesis in cultured mammalian cells (Stich et al., 1978). Although L-ascorbic acid alone was not mutagenic in *Salmonella typhimurium* tester strains TA 98, TA 100, TA 1535, and TA 1537, with or without activation, a freshly prepared mixture of L-ascorbic acid with 1 μM cupric ion was mutagenic in *Salmonella typhimurium* TA 100 (Stich et al., 1978; Heddle and Bruce, 1977; Omura et al., 1978). Ascorbic acid induced sister-chromatid exchange (SCE) in Chinese hamster bone marrow cells in *vitro* (Speit et al., 1980; Stich et al., 1976; Stich et al., 1980) and somatic mutations in Chinese hamster ovary cells *in vitro* (Rosin et al., 1980), but it did not induce SCE in Chinese hamster bone marrow cells *in vivo* (Speit et al., 1980).

An increase in the severity of urothelial lesions including inflammation of the lamina propria and hyperplasia of the transitional epithelium was observed in BALB/c male mice fed diets containing 500 ppm 2-acetylaminofluorene (2-AAF) and given drinking water containing 250 mg/100 ml ascorbic acid, as compared with mice receiving 2-AAF alone and ascorbic acid alone. The interpretation of the observed effects after 28 days is difficult because the mice receiving ascorbic acid drank less water than normally (Frith et

al., 1980). The authors postulated that the effect was probably due to either concentration of urine or decrease in urinary pH. Large doses of ascorbic acid have been shown to reduce urinary pH, whereas sodium ascorbate causes an increase in urinary pH.

Fibrosarcomas and liposarcomas appeared earlier in guinea pigs given a single subcutaneous dose of 20 mg 3-methylcholanthrene followed by daily injections of ascorbic acid (100 mg/kg) for 4 months as compared with guinea pigs that received 20 mg 3-methylcholanthrene alone. There were no controls receiving ascorbic acid only (Banic, 1981). Sodium ascorbate was reported to act as a promoter in nitrosamine-induced preneoplastic lesions in rat bladder epithelium (Ito, 1981).

L-ascorbic acid was tested by the Bioassay Program because of its widespread usage, its popularity as an over-the-counter drug, and lack of adequate carcinogenicity studies.

II. MATERIALS AND METHODS

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Thirteen-Week Studies

TWO-YEAR STUDIES

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Animal Maintenance

Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSES

USP grade L-ascorbic acid was obtained in five lots from ICN Pharmaceuticals, Life Science Division (Cleveland, OH). Lot No. 7290 was used for the 14-day repeated-dose and 13-week studies. Lot Nos. 0371, 2286, and 3993 were used consecutively in the 2-year studies of rats and mice; and Lot No. 4779 was used for the final 2 months of the 2-year study in rats.

Purity and identity analyses were conducted on all lots at Midwest Research Institute (Appendix E) and results were within USP specifications. The results of elemental analyses for carbon and hydrogen agreed with theoretical values for all lots. The purity of L-ascorbic acid (based on iodometric titration) varied from 97.6% for Lot No. 3993 to 101.1% for Lot No. 0371. The results of high-pressure liquid chromatography indicated one impurity (0.25% of the major component) in Lot No. 7290 and two impurities with areas of 0.10% and 0.43% of the major peak in Lot No. 2286. No impurities were detected in the other lots, including Lot 3993. The infrared, ultraviolet, and nuclear magnetic resonance spectra of all lots were consistent with the literature spectra.

L-Ascorbic acid was stored at 4°C. Results of bulk reanalysis at Battelle Columbus Laboratories using USP iodometric titration and infrared absorption analysis indicated no change in any of the lots of L-ascorbic acid throughout the study.

PREPARATION OF TEST DIETS

Test diets were prepared by combining a small amount of Purina® Lab Chow and the required amount of L-ascorbic acid into a premix and then layering this with the remainder of the animal feed. This mixture was then blended for 10 to 15 minutes in a Patterson-Kelly® twin-shell blender. Homogeneity studies at Midwest Research Institute and at Battelle Columbus Laboratories showed that this process gave a homogeneous diet preparation. Prepared diets containing 100,000 ppm L-ascorbic acid were analyzed at Midwest Research Institute and were found to be stable for 2 weeks at temperatures up to 45°C (Appendix F). Test diets were stored in the dark at 23°C for no longer than 1 week. Control animals were fed Purina® Lab Chow.

Randomly selected dosed feed samples from the 2-year studies were analyzed (Appendix G). Results of these analyses and of the referee analysis conducted at Midwest Research Institute indicated that sampled diets were within ± 10% of the desired concentrations.

PRECHRONIC STUDIES

Fourteen-Day Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Portage, MI) and quarantined for 14 days before the study began. Animals were approximately 6 weeks old when placed on study.

Groups of five males and five females of each species were fed diets containing 0, 6,000, 12,500, 25,000, 50,000, or 100,000 ppm L-ascorbic acid for 14 days. Test diets were prepared several days before the start of the study as described previously.

Animals were housed five per cage and received water and feed *ad libitum*. Details of animal maintenance are presented in Table 1. Rats and mice were observed twice daily for mortality and were weighed by cage on days 1 and 15. Necropsies were performed on all animals on day 15 or 16.

Thirteen-Week Studies

Studies were conducted to evaluate the toxicity of cumulative administration of L-ascorbic acid and to determine the concentrations to be used in the 2-year studies.

In the first 13-week study, four-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries (Greenfield, IN). Rats and mice were housed five per cage in polycarbonate cages. Rack shelves were covered with spun-bonded polyester filters (Table 1).

Test diets consisted of Purina® Lab Chow and the required amount of L-ascorbic acid. Control diets consisted of Purina® Lab Chow. Dosed feed, control diets, and water (via an automatic watering system) were available *ad libitum*. Diets containing 0, 25,000, 50,000, or 100,000 ppm L-ascorbic acid were fed to groups of 10 rats and 10 mice of either sex.

Animals were checked for mortality and signs of morbidity twice daily. Those animals that were judged moribund were killed and necropsied. Each animal was given a clinical examination weekly, including palpation for tissue masses or swelling. Body weight and feed consumption data were collected weekly.

At the end of the 91-day study, survivors were killed with carbon dioxide. Necropsies were performed on animals that survived to the end of the study and on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. The following specimens were examined from control and the 100,000 ppm groups: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, bone marrow, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, pituitary, and spinal cord. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

Femoral bone marrow sections were examined from female rats in the controls, 25,000-, 50,000-, and 100,000-ppm groups.

A second 13-week study was conducted to gather additional data on the myelofibrosis observed in female rats in the previous 13-week study. Groups of 20 female F344/N rats were fed diets containing 0, 25,000, or 50,000 ppm L-ascorbic acid for 91 days. Initial and final body weights were measured; samples for hematologic analysis were collected from the orbital sinuses of all animals on days 0, 7, 30, and 90; and bone marrow smears were taken from one femur per animal at necropsy. Both femurs and one rib (including the costochondral junction) were examined microscopically. Details of animal maintenance were similar to those of the first 13-week study (Table 1). Statistical analyses of the hematology data were performed using Dunnett's multiple comparison test (Miller, 1966). Procedures for the hematology analyses are described in Appendix I.

TWO-YEAR STUDIES

Study Design

Diets containing 25,000 or 50,000 ppm L-ascorbic acid were fed to groups of 50 rats and 50 mice of each sex. Controls consisted of 50 untreated rats and 50 untreated mice of each sex.

Source and Specifications of Test Animals

Four-week-old male and female F344/N rats and 5-week-old male and female B6C3F$_1$ mice were obtained from Harlan Industries, observed for 15 days (rats) or 16 days (mice) and then assigned to cages according to a table of random numbers. The cages were then assigned to control and dosed groups according to a second table of random numbers.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages (Table 1). Cages and bedding were replaced twice per week. Dosed feed, control diets, and tap water (via an automatic watering system) were available *ad libitum*. The temperature in the animal rooms was 21°-23°C and the humidity was 40% - 60%. Fifteen changes of room air per hour were provided. Fluorescent lighting provided illumination 12 hours per day.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of morbidity or mortality. Clinical signs were recorded daily. Body weights by cage were recorded every week for the first 13 weeks and monthly thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. The average feed consumption per animal was calculated by dividing the total feed consumption measured for all cages by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the bioassay were killed using carbon dioxide and necropsied.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord.

Necropsies were performed on all animals not autolyzed or cannibalized. 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 in each group. The classification of neoplastic nodules was done according to the recommendations of Squire and Levitt (1975) and the National Academy of Sciences (1980). When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechniques were evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by an experienced pathologist. Slides of all target tissues and those on which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative slides selected by the PWG Chairperson were reviewed blindly by the PWG's experienced pathologists, who reached a consensus and compared their findings with the original diagnoses. When conflicts were found, the PWG sent the appropriate slides and their comments to the original pathologist for review. (This procedure is described, in part, by Maronpot and Boorman, in press.) The final diagnosis represents a consensus of contractor pathologists and the NTP Pathology Working Group.

Data Recording and Statistical Methods

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, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically 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) extensions of Cox's methods for testing for a dose-related trend. All reported P values for the survival analyses are two-sided.

The incidence of neoplastic or nonneoplastic lesions has been 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 included only those animals for which that 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 numbers of animals necropsied.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high- and low-dosed groups with controls and tests for overall dose-response trends.

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 second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental"; i.e., they were merely observed at autopsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill, and the terminal kill period. The denominators of these proportions were the number of animals actually autopsied during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

In addition to these tests, one other set of statistical analyses was carried out and reported in the tables analyzing primary tumors: the Fisher's exact test for pairwise comparisons and the Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart et al., 1979). These tests were based on the overall proportion of tumor-bearing animals. All reported P values for tumor analyses are one-sided.

For studies in which there is little effect of compound administration 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.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS

	Fourteen-Day Study	Thirteen-Week Study *(a)*	Two-Year Study
Experimental Design			
Size of Test Groups	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	0, 6,000, 12,500, 25,000, 50,000, or 100,000 ppm in feed	0, 25,000, 50,000, or 100,000 ppm in feed	0, 25,000, or 50,000 ppm in feed
Duration of Dosing	14 days; killed on day 15 or 16	94 days; killed on day 95 (dosed) and day 92 (controls)	103 weeks
Type and Frequency of Observation	Observed twice daily for morbidity and mortality	Same as 14-day study	Same as 14-day study
Necropsy and Histological Examination	Necropsies performed on all animals; no histopathologic examinations were performed	Necropsies performed on all animals; all controls and all high-dose animals were examined histopathologically; femoral bone marrow of all female rats was examined histopathologically	Necropsies and histopathological examinations performed on all animals
Animals and Animal Maintenance			
Species	F344/N rats; B6C3F$_1$ mice	Same as 14-day study	Same as 14-day study
Animal Source	Charles River Breeding Laboratories (Portage, MI)	Harlan Industries, Inc. (Greenfield, IN)	Same as 13-week study
Time Held Before Start of Test	14 days	Rats: 14 days Mice: 21 days	15-16 days
Age When Placed on Study	6 weeks	Rats: 6 weeks Mice: 7 weeks	Rats: 6 weeks Mice: 8 weeks
Age When Killed	8 weeks	Rats: 19 weeks Mice: 20 weeks	Rats: 111 weeks Mice: 113 weeks

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Fourteen-Day Study	Thirteen-Week Study	Two-Year Study
Method of Animal Distribution	Animals randomized into dosed and control groups by tables of random numbers; distributed by sex into cages and cages distributed from another table to dosed and control groups	Same as 14-day study	Animals of each sex randomized into cage groups, and then cages randomized to dosed and control groups by a table of random numbers
Feed	Purina® Lab Chow, Ralston Purina Co. (Richmond, IN)	Same as 14-day study	Same as 14-day study; feed and feeders changed twice weekly for mice, once weekly for rats
Bedding	Absorb-Dri,® Lab Products, Inc. (Garfield, NJ); changed twice weekly	Same as 14-day study	Same as 14-day study
Water	Automatic watering system, Edstrom Industries (Waterford, WI)	Same as 14-day study	Same as 14-day study
Cages	Polycarbonate, Lab Products, Inc.; changed weekly	Same as 14-day study	Same as 14-day study, but changed twice weekly
Cage Filters	Spun-bonded polyester filter (Dupont 2024)	Same as 14-day study	Same as 14-day study
Animals per Cage	Five	Five	Five
Animal-Room Environment	21°-23°C; 40%-60% relative humidity; 12 hours of fluorescent light per day; 15 room air changes per hour	Same as 14-day study	Same as 14-day study
Other Chemicals on Test in the Same Room	None	None	None

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Fourteen-Day Study	Thirteen-Week Study	Two-Year Study
Chemical/Vehicle Mixture Preparation	Weighed portions of L-ascorbic acid mixed with a weighed portion of Purina® Lab Chow to make up selected doses. Mixture blended for 15 minutes in a Patterson-Kelly® twin-shell V blender	Same as 14-day study	Appropriate quantities of L-ascorbic acid mixed with Purina Lab® Chow and mixed in blender as in 14-day study, but for only 10 minutes
Maximum Storage Time	Mixed 2 days before week of use	Same as 14-day study	One week
Storage Conditions	Stored at 23°C	Same as 14-day study	Stored in air-tight, opaque plastic pails at 23°±1°C

(a) A second 13-week study was conducted in female rats only, for the purpose of collecting an extensive hematological profile. Details of animal maintenance were similar to those of the first 13-week study.

III. RESULTS

RATS

PRECHRONIC STUDIES

Fourteen-Day Studies

Thirteen-Week Studies

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

PRECHRONIC STUDIES

Fourteen-Day Studies

Thirteen-Week Studies

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

PRECHRONIC STUDIES

Fourteen-Day Studies

All animals survived to the end of the dosing period. Depression in mean body weight gain relative to controls was greater than 10% in all dosed groups of male rats except those fed diets containing 25,000 ppm L-ascorbic acid (Table 2). Weight gains for dosed female rats were greater than 17% compared with controls, except in the 6,000 ppm group (+8%) and the 25,000 ppm group (-12%). Weight gain differences were considered to be unrelated to compound administration. No compound-related clinical signs or gross or microscopic pathologic effects were observed.

Thirteen-Week Studies

No rats died in the first 13-week study (Table 3). Mean body weight gains were unchanged for male rats and were depressed 13%-16% among female rats fed diets containing 25,000 ppm or more L-ascorbic acid. Feed consumption by dosed rats of each sex was higher than that of the controls.

Alterations of the femur bone marrow—reticulum-cell hyperplasia (originally diagnosed as myelofibrosis)—were observed in 2/10 females receiving 25,000 ppm, in 1/10 females receiving 50,000 ppm, and in 4/10 females receiving 100,000 ppm; these changes were not seen in female controls or in any groups of males. Myeloid depletion was observed in 2/10 females receiving 50,000 ppm and in 4/10 females receiving 100,000 ppm.

The femoral bone marrow lesion was characterized by multiple foci of cells that appeared to be proliferating fibroblasts replacing the normal myeloid elements and fat cells of the marrow. These cells were loosely arranged, irregular in shape, and medium sized with ill-defined, faintly eosinophilic cytoplasm. They had elongated to oval, hypochromatic nuclei with small or no nucleoli. In some cases, they appeared to contain a faintly eosinophilic fibrillar material. A few somewhat nodular groups of lymphocytes were observed in association with these foci of cells in the two most affected rats in the 100,000 ppm group. Some residual myeloid elements in the cellular foci were observed in all the affected rats in the 50,000 or 100,000 ppm groups, while in two animals in the 25,000 ppm groups the myeloid elements appeared normal, but the lipocytes were absent.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING L-ASCORBIC ACID FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Differential Relative to Controls *(b)* (Percent)
		Initial	Final	Change	
MALES					
0	5/5	101.6	158.4	+56.8	
6,000	5/5	96.8	123.0	+26.2	-54
12,500	5/5	103.2	153.8	+50.6	-11
25,000	5/5	96.2	149.4	+53.2	- 6
50,000	5/5	97.4	142.2	+44.8	-21
100,000	5/5	96.0	141.8	+45.8	-19
FEMALES					
0	5/5	85.6	114.2	+28.6	
6,000	5/5	84.6	115.4	+30.8	+ 8
12,500	5/5	85.6	119.2	+33.6	+17
25,000	5/5	88.2	113.4	+25.2	-12
50,000	5/5	87.6	121.4	+33.8	+18
100,000	5/5	88.2	125.6	+37.4	+31

(a) Number surviving/number per group

(b) Weight Differential Relative to Controls ◘

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING L-ASCORBIC ACID FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Differential Relative to Controls *(c)* (Percent)	Average Daily Feed Consumption (grams)
		Initial	Final	Change *(b)*		
Males						
0	10/10	119.1 ± 1.5	299.6 ± 6.4	+180.5 ± 6.7		15.6
25,000	10/10	113.5 ± 1.4	303.8 ± 7.1	+190.3 ± 6.7	+5.4	16.4
50,000	10/10	114.7 ± 2.2	291.7 ± 5.2	+177.0 ± 5.1	-1.9	16.3
100,000	10/10	112.3 ± 2.8	287.4 ± 7.3	+175.1 ± 5.5	-3.0	16.6
Females						
0	10/10	99.4 ± 2.8	182.2 ± 4.3	+82.8 ± 2.9		11.5
25,000	10/10	97.5 ± 2.2	168.7 ± 7.8	+71.2 ± 6.6	-14.0	12.9
50,000	10/10	94.7 ± 2.7	166.2 ± 2.8	+71.5 ± 1.8	-13.6	13.1
100,000	10/10	90.9 ± 1.7	160.7 ± 4.8	+69.8 ± 3.8	-15.7	13.6

(a) Number surviving/number initially in the group.
(b) Mean weight change of the group ± standard error of the mean
(c) Weight Differential Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

All animals in the second 13-week study survived to the end. Mean body weight gain was depressed by 13% among female rats fed diets containing 50,000 ppm L-ascorbic acid (Table 4).

Although some mean corpuscular hemoglobin concentration values were lower in dosed groups than in controls, no consistent statistical differences were observed, and the results of hematologic analyses were within the clinically normal range for all groups of animals (Table 5). Mild reticulum cell hyperplasia was found in the bone marrow of 2/20 females receiving 25,000 ppm and in 2/20 females receiving 50,000 ppm. Foci of reticulum cells were found in 2/20 females receiving 50,000 ppm.

Doses selected for the rats of both sexes for the 2-year study were 25,000 and 50,000 ppm, the maximum concentration of a test substance in feed recommended in the guidelines of the Bioassay Program. The femoral lesions noted in the female rats were not considered to be potentially life threatening.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF FEMALE RATS FED DIETS CONTAINING L-ABSORBIC ACID IN THE SECOND 13-WEEK STUDY

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Differential Relative to Controls *(c)* (Percent)	Average Daily Feed Consumption (Grams)
		Initial	Final	Change *(b)*		
0	20/20	78.0 ± 2.7	162.7 ± 4.1	+84.7 ± 2.9		10.8
25,000	20/20	84.0 ± 2.2	167.0 ± 3.1	+83.0 ± 3.7	- 2.0	11.3
50,000	20/20	79.6 ± 2.2	153.0 ± 3.9	+73.4 ± 3.0	-13.3	11.8

(a) Number surviving/number initially in the group
(b) Mean weight change of the group ± standard error of the mean
(c) Weight Differential Relative to Controls ◘

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

TABLE 5. SUMMARY OF HEMATOLOGY DATA ON FEMALE RATS FED DIETS CONTAINING L-ASCORBIC ACID IN THE SECOND 13-WEEK STUDY *(a)*

Determination	Dose (ppm)	Days on Study 0	7	30	90
Mean Corpuscular Volume (μ^3)	0	58.0 ± 1.6	58.2 ± 2.7	55.1 ± 1.7	53.7 ± 2.1
	25,000	58.3 ± 1.2	59.1 ± 2.6	55.1 ± 1.4	53.7 ± 1.1
	50,000	60.5 ± 1.3 *(b)*	59.8 ± 3.3	54.8 ± 1.6	53.4 ± 0.6
Mean Corpuscular Hemoglobin (10^{-12}g/red cell)	0	20.5 ± 0.3	21.3 ± 0.6	20.1 ± 0.5	18.9 ± 0.6
	25,000	20.5 ± 0.5	21.1 ± 0.7	19.5 ± 0.3 *(b)*	18.9 ± 0.3
	50,000	20.4 ± 0.5	21.1 ± 0.9	19.9 ± 0.6	19.1 ± 0.2
Mean Corpuscular Hemoglobin Concentration (%)	0	35.4 ± 0.7	36.6 ± 1.5	36.5 ± 1.2	35.3 ± 1.8
	25,000	35.2 ± 0.9	35.7 ± 0.6 *(c)*	35.4 ± 0.8 *(b)*	35.3 ± 0.8
	50,000	33.8 ± 0.7 *(b)*	35.3 ± 0.7 *(b)*	36.4 ± 0.6	35.7 ± 0.5
Platelets (10^5/mm^3)	0	4.67 ± 1.09	3.68 ± 0.69	3.29 ± 0.53	4.01 ± 0.69
	25,000	4.52 ± 1.16	4.27 + 0.85	3.68 ± 0.74	4.10 ± 0.75
	50,000	4.55 ± 1.03	4.44 ± 1.43 *(b)*	3.71 ± 1.09	3.48 ± 0.41 *(c)*
Reticulocytes (% of red cells)	0	5.83 ± 2.80	13.37 ± 4.96	0.74 ± 0.59	1.73 ± 0.85
	25,000	5.67 ± 3.64	13.80 ± 4.71	0.93 ± 0.66	1.96 ± 0.96
	50,000	4.67 ± 1.95	11.78 ± 2.20	0.45 ± 0.37	1.92 ± 1.07
Hemoglobin (g/100 ml)	0	14.03 ± 1.77	15.55 ± 0.84	17.80 ± 0.59	16.83 ± 0.59
	25,000	13.31 ± 2.20	15.57 ± 0.67	17.54 ± 0.77	16.54 ± 0.61
	50,000	13.00 ± 2.39	15.68 ± 0.53	17.33 ± 0.73	17.72 ± 2.25
Packed Cell Volume (%)	0	40.3 ± 4.6	43.5 ± 2.2	49.1 ± 2.1	47.9 ± 3.0
	25,000	38.3 ± 5.8	44.0 ± 1.8	50.1 ± 2.1	46.1 ± 2.1
	50,000	39.2 ± 7.5	44.8 ± 1.9	48.1 ± 2.3	49.0 ± 6.4
RBC Totals (10^6/mm^3)	0	6.85 ± 0.87	7.32 + 0.45	8.85 ± 0.29	8.89 ± 0.37
	25,000	6.48 ± 1.04	7.39 ± 0.42	8.99 ± 0.37	8.74 ± 0.36
	50,000	6.37 ± 1.15	7.43 ± 0.37	8.72 ± 0.52	9.28 ± 1.13

TABLE 5. SUMMARY OF HEMATOLOGY DATA ON FEMALE RATS FED DIETS CONTAINING L-ASCORBIC ACID IN THE SECOND 13-WEEK STUDY *(a)* (Continued)

Determination	Dose (ppm)	Days on Study 0	7	30	90
WBC Totals	0	5.93 ± 1.37	7.52 ± 1.73	7.54 ± 1.50	7.11 ± 1.76
($10^3/mm^3$)	25,000	6.42 ± 1.59	7.92 ± 1.72	7.35 ± 1.06	6.77 ± 1.22
	50,000	5.67 ± 1.46	7.96 ± 1.44	7.21 ± 1.18	8.41 ± 2.61
Differential WBC Count	0	960.5 ± 335.0	1456.4 ± 578.2	1058.0 ± 443.2	1139.0 ± 273.7
Segmented Neutrophils	25,000	960.0 ± 353.1	1636.8 ± 643.3	861.3 ± 309.3	1298.9 ± 591.9
	50,000	915.6 ± 438.9	1462.9 ± 535.2	878.3 ± 347.3	1547.0 ± 695.6 *(c)*
Eosinophils	0	48.8 ± 55.1	30.4 ± 50.5	85.5 ± 80.2	39.2 ± 66.5
	25,000	34.7 ± 51.9	37.3 ± 50.2	73.7 ± 67.3	35.5 ± 65.5
	50,000	29.9 ± 41.7	20.9 ± 37.1	51.0 ± 68.6	52.3 ± 69.2
Lymphocytes	0	4.9 ± 1.4	6.0 ± 1.7	6.4 ± 1.3	5.9 ± 1.7
(10^3)	25,000	5.4 ± 1.7	6.2 ± 1.5	6.4 ± 1.0	5.4 ± 1.0
	50,000	4.8 ± 1.2	6.5 ± 1.3	6.3 ± 1.1	7.0 ± 2.0
Monocytes	0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	25,000	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	50,000	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	8.2 ± 24.3
Band Cells	0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	3.9 ± 17.4
	25,000	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	50,000	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Basophils	0	3.4 ± 15.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	25,000	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	50,000	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

(a) All entries represent the mean (± standard deviation) of 20 samples. P values were determined using Dunnett's multiple comparison test (Miller, 1966) to compare dosed groups with controls at the same time intervals.
(b) $P \leq 0.01$ versus controls
(c) $P \leq 0.05$ versus controls

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and control male rats were similar throughout the study. Mean body weights of dosed female rats were lower than those of the controls during the second year of the study (Figure 1 and Table 6). The average daily feed consumption per rat by low- and high-dose rats was 101% and 105% that of the controls for males (Table 7) and 97% and 98% for females (Table 8). No compound-related clinical signs were observed.

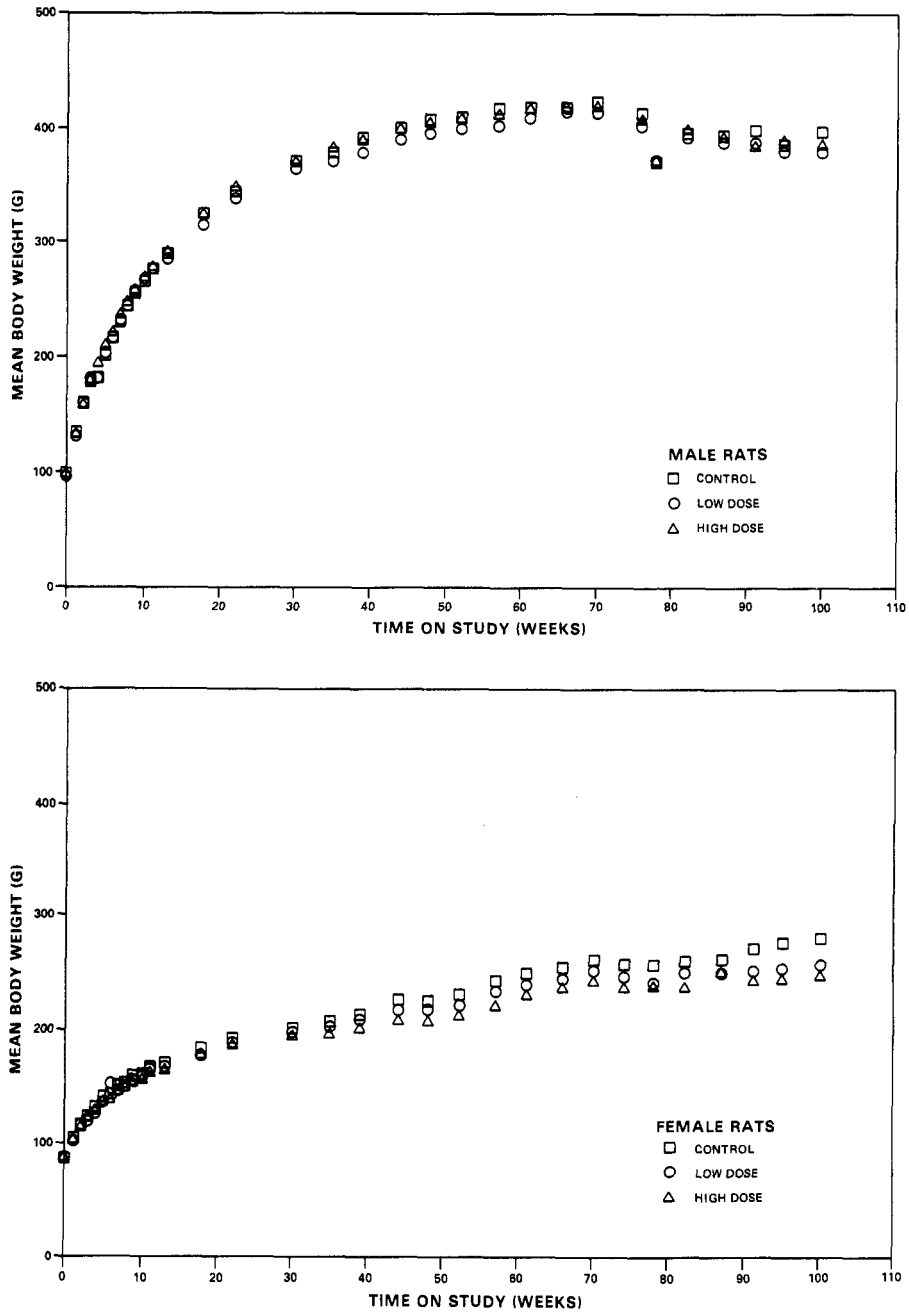

Figure 1. Growth Curves for Rats Fed Diets Containing L-Ascorbic Acid

TABLE 6. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF RATS FED DIETS CONTAINING L-ASCORBIC ACID IN THE 2-YEAR STUDY

		Cumulative Mean Body Weight Change (grams)			Weight Differential Relative to Controls *(a)* (percent)	
	Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males	0	99 *(b)*	97 *(b)*	99 *(b)*		
	1	36	35	35	- 3	- 3
	22	246	241	250	- 2	+ 2
	39	294	282	292	- 4	- 1
	61	321	315	321	- 2	0
	82	298	296	301	- 1	+ 1
	100	299	283	288	- 5	- 4
		398 *(c)*	380 *(c)*	387 *(c)*	- 5 *(d)*	- 3 *(d)*
Females	0	87 *(b)*	88 *(b)*	88 *(b)*		
	1	18	15	16	-17	-11
	22	106	100	98	- 6	- 8
	39	126	121	114	- 4	-10
	61	163	151	142	- 7	-13
	82	173	162	149	- 6	-14
	100	193	169	157	-12	-19
		280 *(c)*	257 *(c)*	245 *(c)*	- 8 *(d)*	-13 *(d)*

(a) Weight Differential Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial weight
(c) Mean body weight at week 100
(d) Mean body weight relative to controls

TABLE 7. FEED AND COMPOUND CONSUMPTION BY MALE RATS FED DIETS CONTAINING L-ASCORBIC ACID IN THE 2-YEAR STUDY

	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)*
2	17.4	161	17.6	161	1.0	2.728	17.6	160	1.0	5.491
6	18.3	216	17.3	216	0.9	2.001	15.9	221	0.9	3.588
10	16.7	265	16.3	267	1.0	1.525	15.0	268	0.9	2.799
13	14.7	290	15.3	285	1.0	1.341	16.1	292	1.1	2.764
18	16.4	325	18.3	315	1.1	1.451	16.3	325	1.0	2.505
22	15.7	345	13.9	338	0.9	1.025	15.1	349	1.0	2.169
30	15.3	372	14.9	364	1.0	1.020	15.7	372	1.0	2.112
35	16.4	379	15.4	372	0.9	1.037	17.4	384	1.1	2.269
39	18.4	393	18.0	379	1.0	1.187	19.9	391	1.1	2.539
44	17.9	403	18.6	392	1.0	1.184	21.9	403	1.2	2.712
48	19.1	409	18.4	396	1.0	1.163	20.6	407	1.1	2.527
52	21.0	412	19.4	401	0.9	1.211	19.4	412	0.9	2.358
57	14.0	418	17.0	404	1.2	1.052	11.3	414	0.8	1.363
61	18.7	420	17.4	412	0.9	1.058	18.1	420	1.0	2.160
66	18.3	420	16.3	416	0.9	0.979	16.3	421	0.9	1.934
70	17.4	424	17.0	415	1.0	1.024	17.4	422	1.0	2.065
76	18.6	415	17.1	403	0.9	1.063	20.1	409	1.1	2.462
78	16.4	371	17.4	372	1.1	1.171	21.9	372	1.3	2.938
82	14.6	397	13.9	393	1.0	0.881	17.9	400	1.2	2.232
87	19.7	395	16.6	388	0.8	1.068	18.6	394	0.9	2.357
91	15.4	400	18.3	388	1.2	1.178	19.6	386	1.3	2.535
95	16.4	387	21.3	381	1.3	1.397	20.0	390	1.2	2.564
100	14.7	398	17.1	380	1.2	1.128	18.9	387	1.3	2.436
Mean	17.0	366	17.1	358	1.0	1.255	17.9	365	1.1	2.560
SD *(d)*	1.8		1.7		0.1	0.398	2.5		0.1	0.763
CV *(e)*	10.6		9.9		10.0	31.7	14.0		9.1	29.8

(a) Grams of feed consumed per animal per day
(b) Grams of feed per day for the dosed group divided by the same value for the controls
(c) Grams of compound consumed per day per kg of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) x 100

TABLE 8. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS FED DIETS CONTAINING L-ASCORBIC ACID IN THE 2-YEAR STUDY

Week	Control		Low-Dose				High-Dose			
	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)*
2	13.7	117	12.1	117	0.9	2.595	13.0	115	0.9	5.652
6	13.1	143	13.0	154	1.0	2.110	11.4	138	0.9	4.141
10	11.7	162	10.6	160	0.9	1.652	10.4	158	0.9	3.300
13	10.1	170	9.6	167	0.9	1.433	9.4	165	0.9	2.857
18	8.3	184	9.9	177	1.2	1.392	9.9	178	1.2	2.769
22	10.0	193	9.6	188	1.0	1.273	9.7	186	1.0	2.611
30	10.9	203	10.4	198	1.0	1.317	10.6	195	1.0	2.711
35	11.6	207	10.4	203	0.9	1.284	11.1	197	1.0	2.828
39	11.6	213	11.6	209	1.0	1.384	9.7	202	0.8	2.405
44	13.0	226	13.3	217	1.0	1.531	13.6	209	1.0	3.247
48	13.1	225	13.6	217	1.0	1.564	13.1	208	1.0	3.159
52	14.4	231	12.4	222	0.9	1.400	12.9	213	0.9	3.018
57	14.9	243	12.4	234	0.8	1.328	14.1	222	1.0	3.185
61	15.6	250	14.1	239	0.9	1.479	14.9	230	1.0	3.230
66	13.4	255	12.9	245	1.0	1.312	12.9	237	1.0	2.712
70	12.9	262	11.9	252	0.9	1.176	11.9	242	0.9	2.450
76	14.6	257	13.4	247	0.9	1.359	13.6	237	0.9	2.863
78	11.4	257	14.6	241	1.3	1.512	13.1	238	1.2	2.761
82	10.3	260	9.6	250	0.9	0.957	11.9	237	1.2	2.502
87	13.6	262	13.1	250	1.0	1.314	14.3	251	1.1	2.846
91	13.4	272	13.0	252	1.0	1.290	13.3	243	1.0	2.734
95	15.0	276	16.1	254	1.1	1.589	14.6	245	1.0	2.974
100	13.1	280	13.3	257	1.0	1.292	15.9	247	1.2	3.210
Mean	12.6	224	12.2	215	1.0	1.458	12.4	208	1.0	3.051
SD *(d)*	1.9		1.8		0.1	0.326	1.8		0.1	0.677
CV *(e)*	15.1		14.8		10.0	22.4	14.5		10.0	22.2

(a) Grams of feed consumed per animal per day
(b) Grams of feed per day for the dosed group divided by the same value for the controls
(c) Grams of compound consumed per day per kg of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) x 100

Survival

Estimates of the probabilities of survival of male and female rats fed diets containing ascorbic acid at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 2. The survival of the high-dose male rats was slightly greater than that of the controls (P=0.087); the results of a trend test over all groups of male rats was P=0.057. No other significant differences were observed between any groups of either sex of rats.

In male rats, 33/50 (66%) of the controls, 35/50 (70%) of the low-dose, and 41/50 (82%) of the high-dose group lived to the termination period of the study at 105 weeks. In female rats, 38/50 (76%) of the controls, 36/50 (72%) of the low-dose, and 37/50 (74%) of the high-dose group lived to the termination period of the study at 105 weeks.

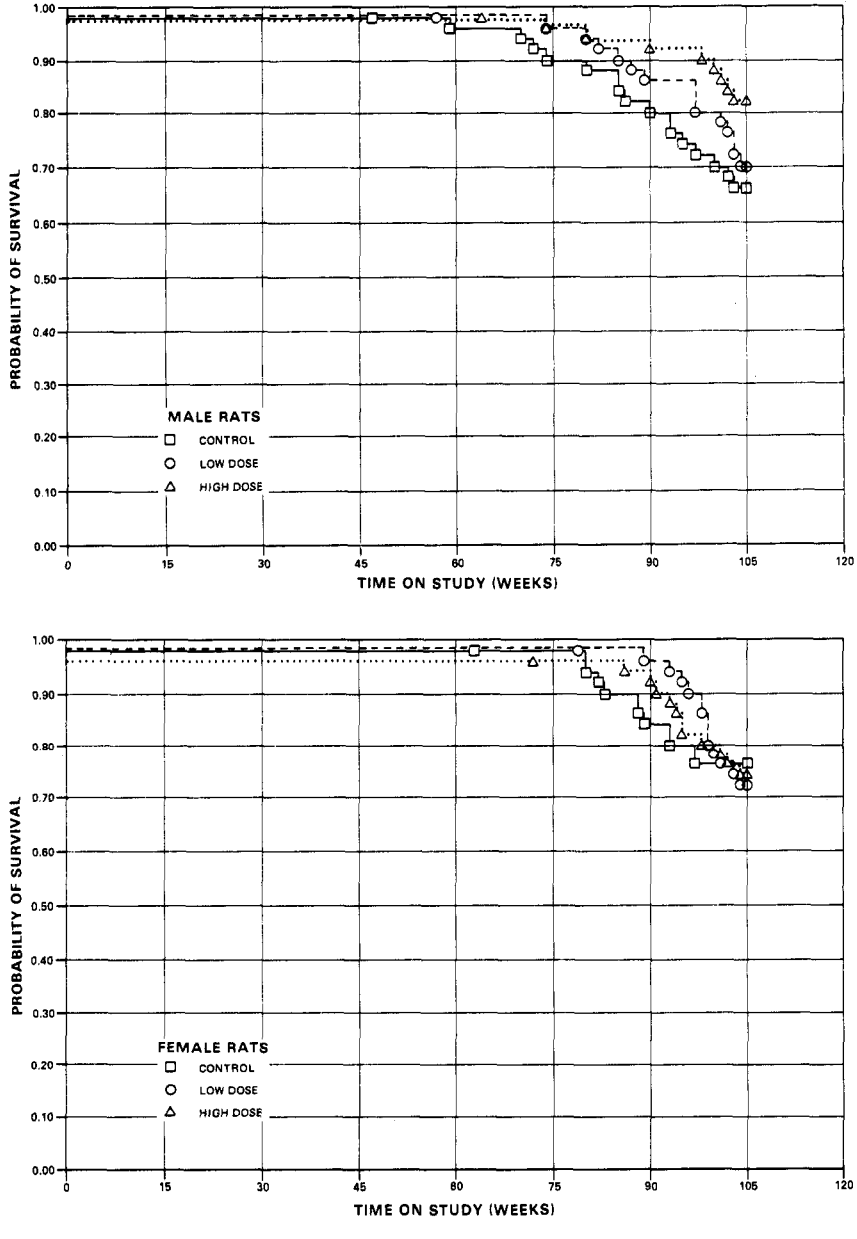

Figure 2. Survival Curves for Rats Fed Diets Containing L-Ascorbic Acid

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give the survival and tumor status for each male and female rat. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Tables 9 and 10 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Hematopoietic System: Pairwise comparisons of low-dose females and controls revealed significantly ($P<0.02$) increased incidences of low-dose females with undifferentiated leukemias (equivalent to mononuclear cell leukemia) (control, 6/50, 12%; low-dose, 17/50, 34%; high-dose, 12/50, 24%). These tumors occurred in increased proportions in high-dose female rats and in slightly decreased proportions in low- and high-dose males (17/50, 16/50, 14/50), but none of the differences were statistically significant.

Preputial or Clitoral Gland: Significant ($P<0.05$) negative trends were observed in the incidence of males with adenocarcinomas of the preputial gland (control, 3/50, 6%; low-dose, 1/50, 2%; high-dose, 0/50, 0%) and of females with adenocarcinomas of the clitoral gland (control, 3/50, 6%; low-dose, 0/50, 0%; high-dose, 0/50, 0%).

Testis: Interstitial-cell tumors occurred with a significant ($P=0.029$, incidental tumor test) negative trend (control, 48/50, 96%; low-dose, 49/50, 98%; high-dose, 46/49, 94%), but none of the pairwise comparisons were statistically significant (incidental tumor test or Fisher's exact test).

Pituitary Gland: Pituitary adenomas showed a decreased trend ($P<0.05$) in dosed females when compared to controls (25/50, 19/50, 15/50); combining adenomas or carcinomas resulted in a significant ($P=0.047$) negative trend between groups only by the incidental tumor trend test (26/50, 20/50, 18/50). No significant differences in incidence were seen for male rats.

TABLE 9. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)*

	Control	Low Dose	High Dose
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall *(b)*	17/50 (34%)	16/50 (32%)	14/50 (28%)
Adjusted *(c)*	39.5%	36.3%	29.6%
Terminal *(d)*	8/33 (24%)	8/35 (23%)	8/41 (20%)
Statistical Tests *(e)*			
Life Table	P=0.152N	P=0.415N	P=0.176N
Incidental Tumor Test	P=0.513N	P=0.577N	P=0.568N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.295N	P=0.500N	P=0.333N
Pituitary: Adenoma or Chromophobe Adenoma			
Tumor Rates			
Overall *(b)*	10/47 (21%)	9/45 (20%)	14/50 (28%)
Adjusted *(c)*	28.4%	26.6%	31.5%
Terminal *(d)*	8/32 (25%)	8/32 (25%)	11/41 (27%)
Statistical Tests *(e)*			
Life Table	P=0.415	P=0.490N	P=0.474
Incidental Tumor Test	P=0.297	P=0.564N	P=0.333
Cochran-Armitage Trend, Fisher Exact Tests	P=0.250	P=0.543	P=0.298
Pituitary: Adenoma, Adenocarcinoma, or Carcinoma			
Tumor Rates			
Overall *(b)*	12/47 (26%)	9/45 (20%)	15/50 (30%)
Adjusted *(c)*	33.0%	26.6%	33.2%
Terminal *(d)*	9/32 (28%)	8/32 (25%)	11/41 (27%)
Statistical Tests *(e)*			
Life Table	P=0.524	P=0.303N	P=0.583
Incidental Tumor Test	P=0.371	P=0.377N	P=0.398
Cochran-Armitage Trend, Fisher Exact Tests	P=0.342	P=0.351N	P=0.396
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	8/49 (16%)	10/50 (20%)	14/50 (28%)
Adjusted *(c)*	21.9%	26.7%	32.3%
Terminal *(d)*	5/33 (15%)	8/35 (23%)	12/41 (29%)
Statistical Tests *(e)*			
Life Table	P=0.224	P=0.461	P=0.267
Incidental Tumor Test	P=0.135	P=0.475	P=0.161
Cochran-Armitage Trend, Fisher Exact Tests	P=0.098	P=0.416	P=0.124
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	2/49 (4%)	4/50 (8%)	6/50 (12%)
Adjusted *(c)*	6.1%	11.0%	14.6%
Terminal *(d)*	2/33 (6%)	3/35 (9%)	6/41 (15%)
Statistical Tests *(e)*			
Life Table	P=0.167	P=0.369	P=0.212
Incidental Tumor Test	P=0.151	P=0.371	P=0.212
Cochran-Armitage Trend, Fisher Exact Tests	P=0.103	P=0.349	P=0.141

TABLE 9. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Thyroid: C-Cell Carcinoma			
Tumor Rates			
Overall *(b)*	4/49 (8%)	2/50 (4%)	2/50 (4%)
Adjusted *(c)*	12.1%	5.3%	4.6%
Terminal *(d)*	4/33 (12%)	1/35 (3%)	1/41 (2%)
Statistical Tests *(e)*			
Life Table	P=0.179N	P=0.305N	P=0.244N
Incidental Tumor Test	P=0.218N	P=0.305N	P=0.282N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.244N	P=0.329N	P=0.329N
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	5/49 (10%)	5/50 (10%)	8/50 (16%)
Adjusted *(c)*	15.2%	13.2%	18.9%
Terminal *(d)*	5/33 (15%)	3/35 (9%)	7/41 (17%)
Statistical Tests *(e)*			
Life Table	P=0.360	P=0.584N	P=0.429
Incidental Tumor Test	P=0.299	P=0.583N	P=0.397
Cochran-Armitage Trend, Fisher Exact Tests	P=0.232	P=0.617N	P=0.290
Preputial Gland: Adenocarcinoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted *(c)*	8.4%	2.9%	0.0%
Terminal *(d)*	2/33 (6%)	1/35 (3%)	0/41 (0%)
Statistical Tests *(e)*			
Life Table	P=0.045N	P=0.287N	P=0.092N
Incidental Tumor Test	P=0.059N	P=0.291N	P=0.141N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.060N	P=0.309N	P=0.121N
Testis: Interstitial-Cell Tumor			
Tumor Rates			
Overall *(b)*	48/50 (96%)	49/50 (98%)	46/49 (94%)
Adjusted *(c)*	100.0%	100.0%	100.0%
Terminal *(d)*	33/33 (100%)	35/35 (100%)	40/40 (100%)
Statistical Tests *(e)*			
Life Table	P=0.016N	P=0.406N	P=0.018N
Incidental Tumor Test	P=0.029N	P=0.610N	P=0.059N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.391N	P=0.500	P=0.490N

(a) Dosed groups received doses of 25,000 or 50,000 ppm of ascorbic acid in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) 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 non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

TABLE 10. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)*

	Control	Low Dose	High Dose
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall *(b)*	6/50 (12%)	17/50 (34%)	12/50 (24%)
Adjusted *(c)*	13.9%	36.9%	27.8%
Terminal *(d)*	3/38 (8%)	8/36 (22%)	7/37 (19%)
Statistical Tests *(e)*			
Life Table	P=0.121	P=0.017	P=0.114
Incidental Tumor Test	P=0.070	P=0.012	P=0.072
Cochran-Armitage Trend, Fisher Exact Tests	P=0.097	P=0.008	P=0.096
Hematopoietic System: Lymphoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted *(c)*	7.2%	4.4%	0.0%
Terminal *(d)*	1/38 (3%)	0/36 (0%)	0/37 (0%)
Statistical Tests *(e)*			
Life Table	P=0.078N	P=0.461N	P=0.122N
Incidental Tumor Test	P=0.053N	P=0.315N	P=0.123N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.082N	P=0.500N	P=0.121N
Pituitary: Adenoma or Chromophobe Adenoma			
Tumor Rates			
Overall *(b)*	25/50 (50%)	19/50 (38%)	15/50 (30%)
Adjusted *(c)*	57.9%	47.2%	38.4%
Terminal *(d)*	20/38 (53%)	15/36 (42%)	13/37 (35%)
Statistical Tests *(e)*			
Life Table	P=0.035N	P=0.197N	P=0.043N
Incidental Tumor Test	P=0.019N	P=0.090N	P=0.025N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.026N	P=0.157N	P=0.033N
Pituitary: Carcinoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted *(c)*	2.6%	5.6%	7.9%
Terminal *(d)*	1/38 (3%)	2/36 (6%)	2/37 (5%)
Statistical Tests *(e)*			
Life Table	P=0.218	P=0.481	P=0.300
Incidental Tumor Test	P=0.238	P=0.481	P=0.359
Cochran-Armitage Trend, Fisher Exact Tests	P=0.222	P=0.500	P=0.309
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	26/50 (52%)	20/50 (40%)	18/50 (36%)
Adjusted *(c)*	60.2%	49.7%	45.0%
Terminal *(d)*	21/38 (55%)	16/36 (44%)	15/37 (41%)
Statistical Tests *(e)*			
Life Table	P=0.083N	P=0.200N	P=0.100N
Incidental Tumor Test	P=0.047N	P=0.092N	P=0.055N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.065N	P=0.158N	P=0.079N

TABLE 10. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Adrenal: Cortical Adenoma			
Tumor Rates			
Overall *(b)*	3/50 (6%) *(f)*	2/50 (4%)	1/49 (2%)
Adjusted *(c)*	7.9%	5.6%	2.7%
Terminal *(d)*	3/38 (8%)	2/36 (6%)	1/37 (3%)
Statistical Tests *(e)*			
Life Table	P=0.231N	P=0.525N	P=0.314N
Incidental Tumor Test	P=0.231N	P=0.525N	P=0.314N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.228N	P=0.500N	P=0.316N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	4/50 (8%)	6/50 (12%)	7/49 (14%)
Adjusted *(c)*	9.7%	15.0%	18.3%
Terminal *(d)*	3/38 (8%)	4/36 (11%)	6/37 (16%)
Statistical Tests *(e)*			
Life Table	P=0.213	P=0.368	P=0.255
Incidental Tumor Test	P=0.274	P=0.335	P=0.315
Cochran-Armitage Trend, Fisher Exact Tests	P=0.204	P=0.370	P=0.251
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	2/49 (4%)	6/50 (12%)	4/49 (8%)
Adjusted *(c)*	5.4%	16.7%	10.1%
Terminal *(d)*	2/37 (5%)	6/36 (17%)	3/37 (8%)
Statistical Tests *(e)*			
Life Table	P=0.294	P=0.124	P=0.345
Incidental Tumor Test	P=0.251	P=0.124	P=0.276
Cochran-Armitage Trend, Fisher Exact Tests	P=0.289	P=0.141	P=0.339
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	2/49 (4%)	7/50 (14%)	5/49 (10%)
Adjusted *(c)*	5.4%	19.4%	12.0%
Terminal *(d)*	2/37 (5%)	7/36 (19%)	3/37 (8%)
Statistical Tests *(e)*			
Life Table	P=0.203	P=0.072	P=0.232
Incidental Tumor Test	P=0.140	P=0.072	P=0.131
Cochran-Armitage Trend, Fisher Exact Tests	P=0.194	P=0.085	P=0.218
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(b)*	5/50 (10%)	6/50 (12%)	8/50 (16%)
Adjusted *(c)*	12.3%	15.8%	18.9%
Terminal *(d)*	3/38 (8%)	5/36 (14%)	4/37 (11%)
Statistical Tests *(e)*			
Life Table	P=0.235	P=0.499	P=0.290
Incidental Tumor Test	P=0.295	P=0.530	P=0.400
Cochran-Armitage Trend, Fisher Exact Tests	P=0.226	P=0.500	P=0.277

TABLE 10. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Clitoral Gland: Adenocarcinoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted *(c)*	7.0%	0.0%	0.0%
Terminal *(d)*	1/38 (3%)	0/36 (0%)	0/37 (0%)
Statistical Tests *(e)*			
Life Table	P=0.038N	P=0.120N	P=0.125N
Incidental Tumor Test	P=0.045N	P=0.110N	P=0.123N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.037N	P=0.121N	P=0.121N
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(b)*	13/50 (26%)	9/50 (18%)	13/50 (26%)
Adjusted *(c)*	33.1%	21.9%	32.1%
Terminal *(d)*	12/38 (32%)	5/36 (14%)	10/37 (27%)
Statistical Tests *(e)*			
Life Table	P=0.534	P=0.262N	P=0.572
Incidental Tumor Test	P=0.539N	P=0.162N	P=0.553
Cochran-Armitage Trend, Fisher Exact Tests	P=0.547	P=0.235N	P=0.590
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(b)*	13/50 (26%)	10/50 (20%)	14/50 (28%)
Adjusted *(c)*	33.1%	24.4%	34.6%
Terminal *(d)*	12/38 (32%)	6/36 (17%)	11/37 (30%)
Statistical Tests *(e)*			
Life Table	P=0.442	P=0.348N	P=0.482
Incidental Tumor Test	P=0.460	P=0.236N	P=0.460
Cochran-Armitage Trend, Fisher Exact Tests	P=0.454	P=0.318N	P=0.500

(a) Dosed groups received doses of 25,000 or 50,000 ppm of ascorbic acid in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) 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 non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).
(f) One carcinoma was also seen in a control.

PRECHRONIC STUDIES

Fourteen-Day Studies

All animals survived to the end of the dosing period. Mice of each sex receiving 100,000 ppm lost weight (Table 11). Females receiving 12,500-50,000 ppm gained only 0-0.2 g. Depressions in mean body weight gains were not dose related in male or female mice that received dietary concentrations between 6,000 and 50,000 ppm.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING L-ASCORBIC ACID FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Differential Relative to Controls *(b)* (Percent)
		Initial	Final	Change	
Males					
0	5/5	22.8	25.0	+2.2	
6,000	5/5	22.8	23.4	+0.6	- 73
12,500	5/5	22.6	23.4	+0.8	- 64
25,000	5/5	21.8	23.4	+1.6	- 27
50,000	5/5	22.8	24.8	+2.0	- 9
100,000	5/5	23.4	22.4	-1.0	-145
Females					
0	5/5	18.2	19.6	+1.4	
6,000	5/5	18.2	19.6	+1.4	0
12,500	5/5	18.6	18.6	0	-100
25,000	5/5	18.6	18.8	+0.2	- 86
50,000	5/5	18.2	18.2	0	-100
100,000	5/5	18.2	18.1	-0.1	-107

(a) Number surviving/number per group

(b) Weight Differential Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

Thirteen-Week Studies

One male mouse receiving 50,000 ppm died on day 84. Mean body weight gain relative to controls was depressed by 37% in males receiving 50,000 or 100,000 ppm (Table 12). Weight gains of dosed and control female mice were not depressed by more than 10% to 13% and were not dose related. Feed consumption by dosed and control mice was comparable.

Cystic endometrial glands were found in the uteri of 4/9 females receiving 100,000 ppm compared with none in the controls. No other compound-related effects were observed.

Doses selected for mice on the 2-year study were 25,000 and 50,000 ppm L-ascorbic acid, the maximum concentration of a test substance in feed recommended in the guidelines of the Bioassay Program.

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING L-ASCORBIC ACID FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Differential Relative to Controls *(c)* (Percent)	Average Daily Feed Consumption (grams)
		Initial	Final	Change *(b)*		
Males						
0	10/10	24.9 ± 0.6	31.4 ± 0.5	+6.5 ± 0.5		6.0
25,000	10/10	27.4 ± 0.6	34.2 ± 0.9	+6.8 ± 0.7	+ 4.6	6.0
50,000	9/10 *(d)*	26.0 ± 0.6	30.1 ± 0.9	+4.1 ± 0.5	-36.9	6.5
100,000	10/10	26.5 ± 0.4	30.6 ± 0.5	+4.1 ± 0.3	-36.9	6.2
Females						
0	10/10	21.4 ± 0.5	26.2 ± 0.6	+4.8 ± 0.3		6.4
25,000	10/10	20.6 ± 0.5	24.9 ± 0.5	+4.3 ± 0.2	-10.4	6.4
50,000	10/10	20.6 ± 0.3	24.8 ± 0.4	+4.2 ± 0.2	-12.5	6.4
100,000	10/10	20.5 ± 0.3	24.7 ± 0.5	+4.2 ± 0.3	-12.5	6.0

(a) Number surviving/number initially in the group

(b) Mean weight change group ± standard error of the mean

(c) Weight Differential Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(d) Died on day 84

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed female mice, but not of male mice, were lower than those of the controls throughout most of the study. Final body weights were comparable; high-dose female mice weighed less than controls at week 103 (-11%) (Figure 3 and Table 13). The average daily feed consumption per mouse by low- and high-dose mice was 104% and 101% that of the controls for males (Table 14) and 102% and 106% for females (Table 15). No other compound-related clinical signs were observed.

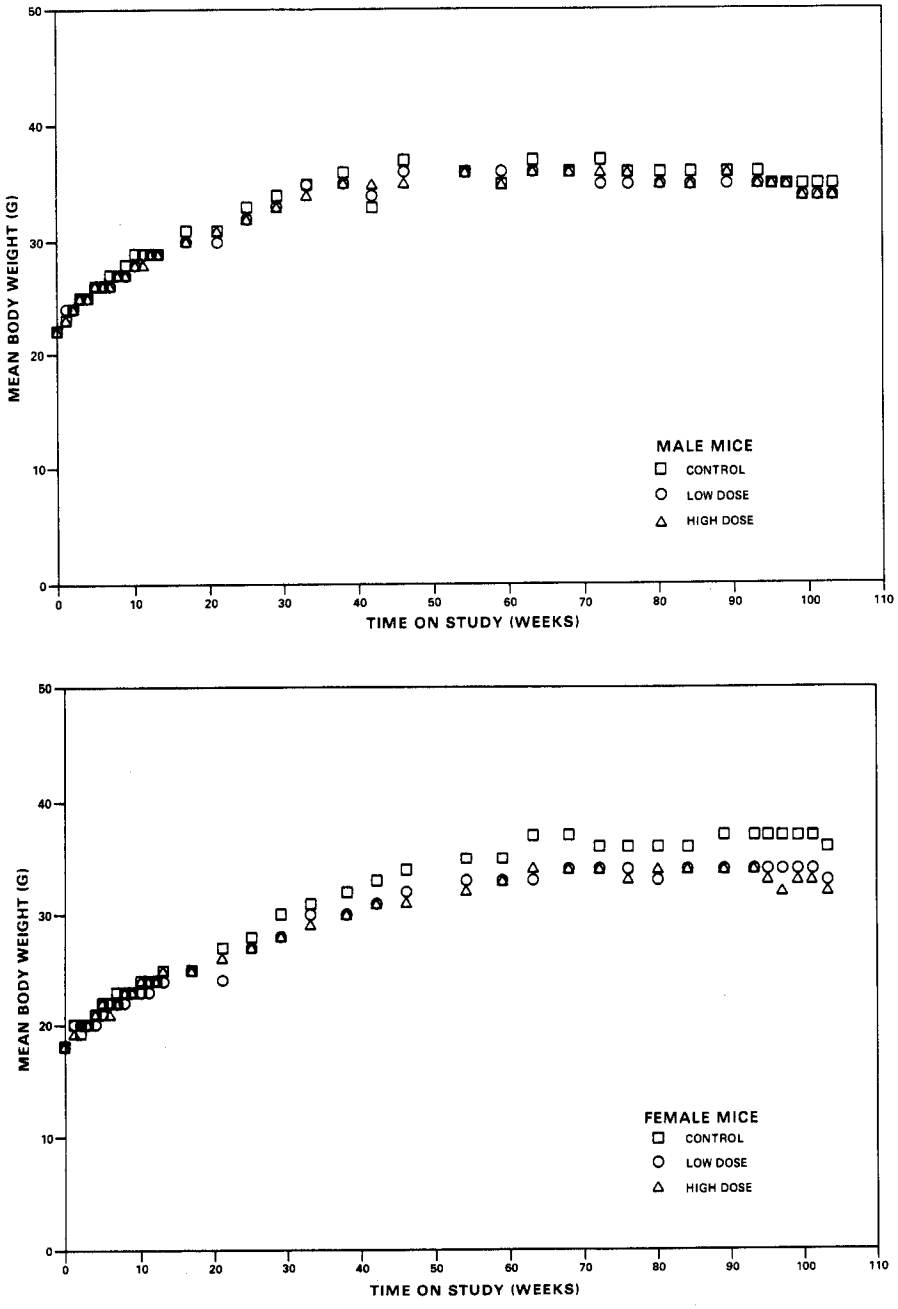

Figure 3. Growth Curves for Mice Fed Diets Containing L-Ascorbic Acid

TABLE 13. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF MICE FED DIETS CONTAINING L-ASCORBIC ACID IN THE 2-YEAR STUDY

		Cumulative Mean Body Weight Change (grams)			Weight Differential Relative to Controls *(a)* (percent)	
	Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males	0	22 *(b)*	22 *(b)*	22 *(b)*		
	1	1	2	1	+100	0
	21	9	8	9	- 11	0
	42	11	12	13	+ 9	+18
	63	15	14	14	- 7	-7
	80	14	13	13	- 7	-7
	101	13	13	12	0	-8
	103	35 *(c)*	34 *(c)*	34 *(c)*	- 3 *(d)*	-3 *(d)*
Females	0	18 *(b)*	18 *(b)*	18*(b)*		
	1	2	2	1	0	-50
	21	9	6	6	- 33	-33
	42	15	13	13	- 13	-13
	63	19	15	16	- 21	-16
	80	18	15	16	- 17	-11
	101	19	16	15	- 16	-21
	103	36 *(c)*	33 *(c)*	32 *(c)*	- 8 *(d)*	-11 *(d)*

(a) Weight Differential Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial weight

(c) Mean body weight at week 103

(d) Weight at week 103 relative to controls

TABLE 14. FEED AND COMPOUND CONSUMPTION BY MALE MICE FED DIETS CONTAINING L-ASCORBIC ACID IN THE 2-YEAR STUDY

	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	6.9	25	6.7	25	1.0	6.714	7.1	25	1.0	14.286
9	7.0	28	7.9	27	1.1	7.275	7.9	27	1.1	14.550
13	7.3	29	7.9	29	1.1	6.773	7.6	29	1.0	13.054
17	6.6	31	7.6	30	1.2	6.310	7.6	30	1.2	12.619
21	7.7	31	8.1	30	1.1	6.786	7.7	31	1.0	12.442
25	7.7	33	8.6	32	1.1	6.696	8.1	32	1.1	12.723
29	7.7	34	8.4	33	1.1	6.385	8.3	33	1.1	12.554
33 *(d)*										
38	9.3	36	8.1	35	0.9	5.816	8.1	35	0.9	11.633
42	8.4	33	7.6	34	0.9	5.567	8.0	35	0.9	11.429
46	8.4	37	8.0	36	0.9	5.556	8.0	35	0.9	11.429
54	8.1	36	8.0	36	1.0	5.556	8.3	36	1.0	11.508
59	8.0	35	8.0	36	1.0	5.556	8.0	35	1.0	11.429
63	8.4	37	8.4	36	1.0	5.853	8.7	36	1.0	12.103
68	8.0	36	8.9	36	1.1	6.151	8.7	36	1.1	12.103
72	8.3	37	8.4	35	1.0	6.020	8.7	36	1.1	12.103
76	8.4	36	8.4	35	1.0	6.020	8.9	36	1.1	12.302
80	8.7	36	9.7	35	1.1	6.939	8.9	35	1.0	12.653
84	9.0	36	9.6	35	1.1	6.837	9.1	35	1.0	13.061
89	8.9	36	9.3	35	1.0	6.633	8.7	36	1.0	12.103
93	8.6	36	9.6	35	1.1	6.837	8.7	35	1.0	12.449
99	8.6	35	9.6	34	1.1	7.038	8.9	34	1.0	13.025
101	9.1	35	9.6	34	1.0	7.038	8.6	34	0.9	12.605
Mean	8.4	34	8.7	33	1.0	6.515	8.5	33	1.0	12.788
SD *(e)*	1.4	3.2	1.3	3.1	0.1	0.849	1.2	3.1	0.1	1.758
CV *(f)*	16.7	9.4	14.9	9.4	10.0	13.0	14.1	9.4	10.0	13.7

(a) Grams of feed consumed per animal per day
(b) Grams of feed per day for the dosed group divided by the same value for the controls
(c) Grams of compound consumed per day per kg of body weight
(d) Values obtained during week 33 were considered unreliable because of spillage
(e) Standard deviation
(f) Coefficient of Variation = (standard deviation/mean) x 100

TABLE 15. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE FED DIETS CONTAINING L-ASCORBIC ACID IN THE 2-YEAR STUDY

	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	6.9	21	7.3	20	1.1	9.107	6.7	21	1.0	15.986
9	7.4	23	7.4	23	1.0	8.075	8.1	23	1.1	17.702
13	7.9	25	8.4	24	1.1	8.780	8.1	25	1.0	16.286
17	6.6	25	7.3	25	1.1	7.286	7.9	25	1.2	15.714
21	7.3	27	7.1	24	1.0	7.440	7.6	26	1.0	14.560
25	7.4	28	8.3	27	1.1	7.672	8.7	27	1.2	16.138
29	7.3	30	8.4	28	1.2	7.526	7.9	28	1.1	14.031
33 *(d)*										
38	8.1	32	8.1	30	1.0	6.786	9.0	30	1.1	15.000
42	8.0	33	8.0	31	1.0	6.452	8.6	31	1.1	13.825
46	8.3	34	8.6	32	1.0	6.696	8.9	31	1.1	14.286
54	8.3	35	7.6	33	0.9	5.736	9.1	32	1.1	14.286
59	8.6	35	7.6	33	0.9	5.736	8.3	33	1.0	12.554
63	8.4	37	8.0	33	0.9	6.061	8.7	34	1.0	12.815
68	9.3	37	9.6	34	1.0	7.038	8.4	34	0.9	12.395
72	8.1	36	8.1	34	1.0	5.987	8.4	34	1.0	12.395
76	8.4	36	8.9	34	1.1	6.513	8.6	33	1.0	12.987
80	8.7	36	8.6	33	1.0	6.494	9.3	34	1.1	13.655
84	8.9	36	9.1	34	1.0	6.723	9.3	34	1.0	13.655
89	8.7	37	8.9	34	1.0	6.513	9.1	34	1.0	13.445
93	8.6	37	9.3	34	1.1	6.828	9.4	34	1.1	13.866
99	8.6	37	9.1	34	1.0	6.723	9.6	33	1.1	14.502
101	8.9	37	9.0	34	1.0	6.618	9.3	37	1.0	12.548
Mean	8.4	32	8.6	30	1.0	7.186	8.9	31	1.1	14.792
SD *(d)*	1.6	5.1	1.6	4.4	0.1	1.443	1.7	4.3	0.1	3.124
CV *(e)*	19.0	15.9	18.6	14.7	10.0	20.1	19.1	13.9	9.1	21.1

(a) Grams of feed consumed per animal per day
(b) Grams of feed per day for the dosed group divided by the same value for the controls
(c) Grams of compound consumed per day per kg of body weight
(d) Values obtained during week 33 were considered unreliable because of spillage
(e) Standard deviation
(f) Coefficient of Variation = (standard deviation/mean) x 100

Survival

Estimates of the probabilities of survival of male and female mice fed diets containing ascorbic acid at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 4. The survival of the high-dose group of male mice was significantly greater than that of the controls (P=0.009), and the trend over all groups of male mice was statistically significant (P=0.005). No other significant differences were observed between any group of either sex of mice.

In male mice, 36/50 (72%) of the controls, 41/50 (82%) of the low-dose, and 47/50 (94%) of the high-dose group lived to the termination period of the study at 105 weeks. In female mice, all groups survived equally (78%) to the termination period of the study at 105 weeks. The survival data include one low-dose female mouse that died during the termination period of the study. For statistical purposes, this mouse has been considered to have been killed during the terminal kill at the end of the study.

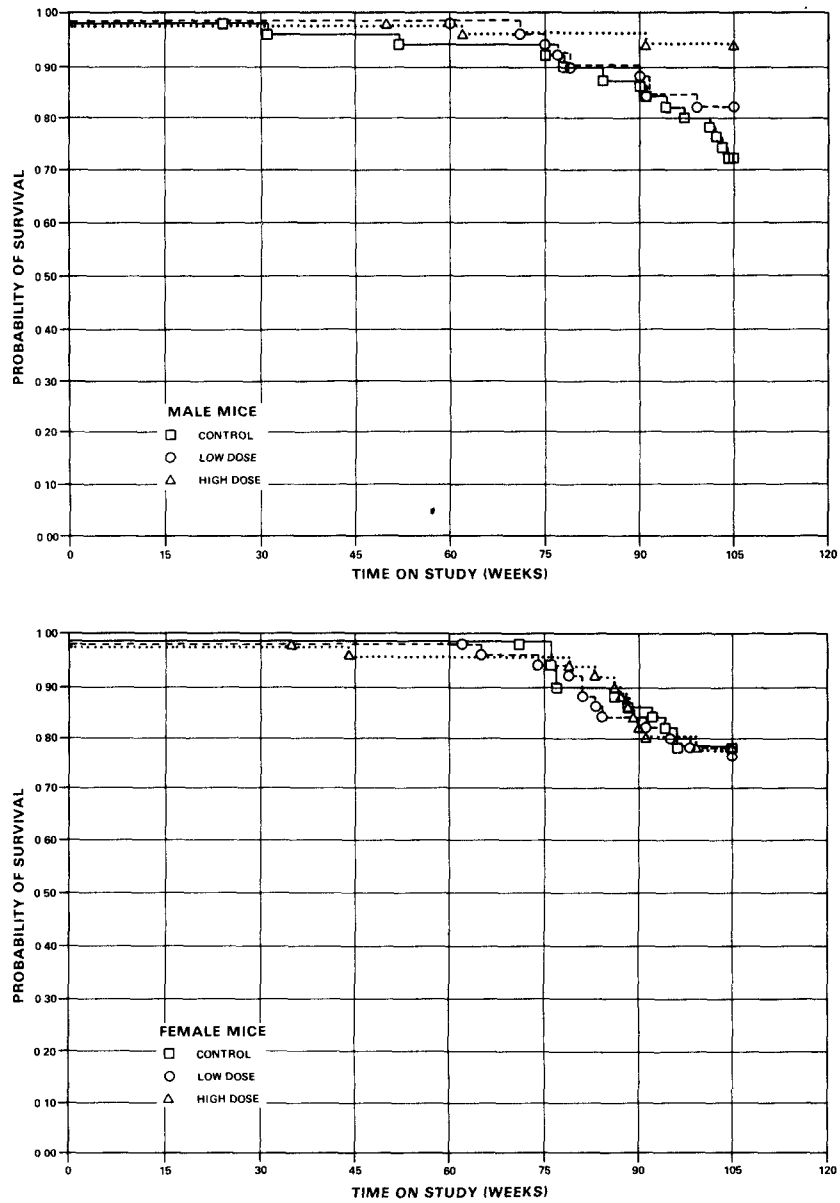

Figure 4. Survival Curves for Mice Fed Diets Containing L-Ascorbic Acid

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms occurring in mice are summarized in Appendix B, Tables B1 and B2; Tables B3 and B4 give the survival and tumor status of each male and female mouse. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Tables 16 and 17 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Circulatory System: The incidence of low-dose male mice with hemangiosarcomas (4/50, 8%) was significantly increased (P=0.047, incidental tumor test) when compared with that of the controls (1/50, 2%). The hemangiosarcomas occurred in liver, bone marrow, and spleen. The incidence in the high-dose males (0/50) was less than that in the controls, and this tumor did not occur in female mice with statistically significant proportions. A hemangioma of the pancreas occurred in a high-dose male mouse.

Hematopoietic System: A statistically significant ($P<0.05$) negative trend occurred in the incidence of female mice with lymphocytic leukemia (control, 3/50, 6%; low-dose, 0/50; high-dose, 0/50). The incidence of females with malignant lymphoma or leukemia was not statistically significant (control, 14/50, 28%; low-dose, 13/50, 26%; high-dose, 17/50, 34%). Significant negative trends were observed in the incidences of male mice with malignant lymphocytic lymphoma (P=0.045, life table; control, 3/50, 6%; low-dose, 1/50, 2%; high-dose, 0/50), all malignant lymphomas (P=0.044, life table; control, 8/50, 16%; low-dose, 7/50, 14%; high-dose, 3/50, 6%), and combined lymphoma or leukemia (P=0.028, life table; control, 9/50, 18%; low-dose, 8/50, 16%; high-dose, 3/50, 6%). The combined incidence of high-dose males with lymphoma or leukemia was significantly lower than that in the controls (P=0.035, life table).

Liver: A statistically significant negative trend occurred in the incidence of male mice with hepatocellular carcinomas (P=0.031, life table), and the incidence in the high-dose group was significantly lower than that in the controls (P=0.032, life table; 10/50, 12/49, 4/50). Combining hepatocellular adenomas or carcinomas resulted in no differences among groups (16/50, 16/49, 13/50).

TABLE 16. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)*

	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	3/49 (6%)	3/49 (6%)	3/49 (6%)
Adjusted *(c)*	8.3%	7.3%	6.4%
Terminal *(d)*	3/36 (8%)	3/41 (7%)	3/47 (6%)
Statistical Tests *(e)*			
Life Table	P=0.450N	P=0.602N	P=0.535N
Incidental Tumor Test	P=0.450N	P=0.602N	P=0.535N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.583	P=0.661	P=0.661
Lung: Alveolar/Bronchiolar Carcinoma			
Tumor Rates			
Overall *(b)*	2/49 (4%)	1/49 (2%)	5/49 (10%)
Adjusted *(c)*	5.0%	2.4%	10.4%
Terminal *(d)*	1/36 (3%)	1/41 (2%)	4/47 (9%)
Statistical Tests *(e)*			
Life Table	P=0.201	P=0.467N	P=0.316
Incidental Tumor Test	P=0.119	P=0.470N	P=0.163
Cochran-Armitage Trend, Fisher Exact Tests	P=0.133	P=0.500N	P=0.218
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	5/49 (10%)	4/49 (8%)	8/49 (16%)
Adjusted *(c)*	13.1%	9.8%	16.7%
Terminal *(d)*	4/36 (11%)	4/41 (10%)	7/47 (15%)
Statistical Tests *(e)*			
Life Table	P=0.365	P=0.427N	P=0.448
Incidental Tumor Test	P=0.287	P=0.428N	P=0.317
Cochran-Armitage Trend, Fisher Exact Tests	P=0.215	P=0.500N	P=0.276
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(b)*	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted *(c)*	7.3%	11.8%	6.4%
Terminal *(d)*	0/36 (0%)	4/41 (10%)	3/47 (6%)
Statistical Tests *(e)*			
Life Table	P=0.452N	P=0.407	P=0.559N
Incidental Tumor Test	P=0.318	P=0.226	P=0.281
Cochran-Armitage Trend, Fisher Exact Tests	P=0.576	P=0.357	P=0.661
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(b)*	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted *(c)*	7.7%	2.4%	0.0%
Terminal *(d)*	2/36 (6%)	0/41 (0%)	0/47 (0%)
Statistical Tests *(e)*			
Life Table	P=0.045N	P=0.279N	P=0.089N
Incidental Tumor Test	P=0.126N	P=0.382N	P=0.141N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.060N	P=0.309N	P=0.121N

TABLE 16. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Hematopoietic System: All Malignant Lymphoma			
Tumor Rates			
Overall *(b)*	8/50 (16%)	7/50 (14%)	3/50 (6%)
Adjusted *(c)*	18.7%	16.2%	6.4%
Terminal *(d)*	3/36 (8%)	5/41 (12%)	3/47 (6%)
Statistical Tests *(e)*			
Life Table	P=0.044N	P=0.431N	P=0.058N
Incidental Tumor Test	P=0.242N	P=0.602N	P=0.296N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.083N	P=0.500N	P=0.100N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	9/50 (18%)	8/50 (16%)	3/50 (6%)
Adjusted *(c)*	20.6%	17.9%	6.4%
Terminal *(d)*	3/36 (8%)	5/41 (12%)	3/47 (6%)
Statistical Tests *(e)*			
Life Table	P=0.028N	P=0.434N	P=0.035N
Incidental Tumor Test	P=0.246N	P=0.588	P=0.296N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.053N	P=0.500N	P=0.061N
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted *(c)*	2.5%	9.5%	0.0%
Terminal *(d)*	0/36 (0%)	3/41 (7%)	0/47 (0%)
Statistical Tests *(e)*			
Life Table	P=0.315N	P=0.212	P=0.468N
Incidental Tumor Test	P=0.514	P=0.047	P=0.824N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.390N	P=0.181	P=0.500N
Liver: Adenoma			
Tumor Rates			
Overall *(b)*	6/50 (12%)	4/49 (8%)	9/50 (18%)
Adjusted *(c)*	16.7%	9.8%	19.1%
Terminal *(d)*	6/36 (17%)	4/41 (10%)	9/47 (19%)
Statistical Tests *(e)*			
Life Table	P=0.402	P=0.289N	P=0.499
Incidental Tumor Test	P=0.402	P=0.289N	P=0.499
Cochran-Armitage Trend, Fisher Exact Tests	P=0.227	P=0.383N	P=0.288
Liver: Carcinoma			
Tumor Rates			
Overall *(b)*	10/50 (20%)	12/49 (24%)	4/50 (8%)
Adjusted *(c)*	24.6%	26.4%	8.5%
Terminal *(d)*	6/36 (17%)	8/41 (20%)	4/47 (9%)
Statistical Tests *(e)*			
Life Table	P=0.031N	P=0.502	P=0.032N
Incidental Tumor Test	P=0.166N	P=0.347	P=0.168N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.074N	P=0.384	P=0.074N

TABLE 16. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	16/50 (32%)	16/49 (33%)	13/50 (26%)
Adjusted *(c)*	39.7%	35.3%	27.7%
Terminal *(d)*	12/36 (33%)	12/41 (29%)	13/47 (28%)
Statistical Tests *(e)*			
Life Table	P=0.101N	P=0.447N	P=0.112N
Incidental Tumor Test	P=0.319N	P=0.580N	P=0.322N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.293N	P=0.558	P=0.330N

(a) Dosed groups received doses of 25,000 or 50,000 ppm of ascorbic acid in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) 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 non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

TABLE 17. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)*

	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	1/49 (2%)	4/49 (8%)	1/50 (2%)
Adjusted *(c)*	2.6%	10.3%	2.6%
Terminal *(d)*	1/38 (3%)	4/39 (10%)	1/39 (3%)
Statistical Tests *(e)*			
Life Table	P=0.591N	P=0.187	P=0.756N
Incidental Tumor Test	P=0.591N	P=0.187	P=0.756N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.593N	P=0.181	P=0.747N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(b)*	5/50 (10%)	4/50 (8%)	6/50 (12%)
Adjusted *(c)*	11.4%	9.8%	15.0%
Terminal *(d)*	2/39 (5%)	3/39 (8%)	5/39 (13%)
Statistical Tests *(e)*			
Life Table	P=0.438	P=0.509N	P=0.503
Incidental Tumor Test	P=0.338	P=0.470N	P=0.295
Cochran-Armitage Trend, Fisher Exact Tests	P=0.434	P=0.500N	P=0.500
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(b)*	5/50 (10%)	6/50 (12%)	3/50 (6%)
Adjusted *(c)*	12.4%	14.9%	6.9%
Terminal *(d)*	4/39 (10%)	5/39 (13%)	1/39 (3%)
Statistical Tests *(e)*			
Life Table	P=0.310N	P=0.497	P=0.361N
Incidental Tumor Test	P=0.237N	P=0.517	P=0.296N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.303N	P=0.500	P=0.357N
Hematopoietic System: All Malignant Lymphoma			
Tumor Rates			
Overall *(b)*	11/50 (22%)	13/50 (26%)	16/50 (32%)
Adjusted *(c)*	25.2%	30.8%	36.9%
Terminal *(d)*	7/39 (18%)	10/39 (26%)	12/39 (31%)
Statistical Tests *(e)*			
Life Table	P=0.169	P=0.405	P=0.202
Incidental Tumor Test	P=0.135	P=0.420	P=0.132
Cochran-Armitage Trend, Fisher Exact Tests	P=0.154	P=0.408	P=0.184
Hematopoietic System: Lymphocytic Leukemia			
Tumor Rates			
Overall *(b)*	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted *(c)*	7.7%	0.0%	0.0%
Terminal *(d)*	3/39 (8%)	0/39 (0%)	0/39 (0%)
Statistical Tests *(e)*			
Life Table	P=0.037N	P=0.121N	P=0.121N
Incidental Tumor Test	P=0.037N	P=0.121N	P=0.121N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.037N	P=0.121N	P=0.121N

TABLE 17. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Hematopoietic System: Leukemia			
Tumor Rates			
Overall *(b)*	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted *(c)*	7.7%	0.0%	2.1%
Terminal *(d)*	3/39 (8%)	0/39 (0%)	0/39 (0%)
Statistical Tests *(e)*			
Life Table	P=0.174N	P=0.121N	P=0.301N
Incidental Tumor Test	P=0.129N	P=0.121N	P=0.225N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.176N	P=0.121N	P=0.309N
Hematopoietic System: Malignant Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	14/50 (28%)	13/50 (26%)	17/50 (34%)
Adjusted *(c)*	32.2%	30.8%	38.2%
Terminal *(d)*	10/39 (26%)	10/39 (26%)	12/39 (31%)
Statistical Tests *(e)*			
Life Table	P=0.306	P=0.508N	P=0.349
Incidental Tumor Test	P=0.292	P=0.486N	P=0.305
Cochran-Armitage Trend, Fisher Exact Tests	P=0.291	P=0.500N	P=0.333
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	1/50 (2%)	5/50 (10%)
Adjusted *(c)*	5.1%	2.6%	12.5%
Terminal *(d)*	2/39 (5%)	1/39 (3%)	4/39 (10%)
Statistical Tests *(e)*			
Life Table	P=0.135	P=0.500N	P=0.220
Incidental Tumor Test	P=0.102	P=0.500N	P=0.161
Cochran-Armitage Trend, Fisher Exact Tests	P=0.133	P=0.500N	P=0.218
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	1/49 (2%)	3/50 (6%)
Adjusted *(c)*	7.7%	2.6%	7.2%
Terminal *(d)*	3/39 (8%)	1/39 (3%)	2/39 (5%)
Statistical Tests *(e)*			
Life Table	P=0.592N	P=0.305N	P=0.660N
Incidental Tumor Test	P=0.539N	P=0.305N	P=0.592N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.593	P=0.316N	P=0.661
Pituitary: Adenoma, Chromophobe Adenoma, or Carcinoma			
Tumor Rates			
Overall *(b)*	3/43 (7%)	2/42 (5%)	1/47 (2%)
Adjusted *(c)*	8.4%	4.2%	2.6%
Terminal *(d)*	2/33 (6%)	0/33 (0%)	1/38 (3%)
Statistical Tests *(e)*			
Life Table	P=0.206N	P=0.502N	P=0.272N
Incidental Tumor Test	P=0.282N	P=0.561N	P=0.326N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.197N	P=0.511N	P=0.275N

TABLE 17. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(b)*	3/50 (6%)	2/48 (4%)	0/50 (0%)
Adjusted *(c)*	7.3%	5.1%	0.0%
Terminal *(d)*	2/39 (5%)	2/39 (5%)	0/39 (0%)
Statistical Tests *(e)*			
Life Table	P=0.085N	P=0.504N	P=0.127N
Incidental Tumor Test	P=0.058N	P=0.454N	P=0.070N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.083N	P=0.520N	P=0.121N

(a) Dosed groups received doses of 25,000 or 50,000 ppm of ascorbic acid in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) 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 non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

IV. DISCUSSION AND CONCLUSIONS

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Rats and mice synthesize their own ascorbic acid. Humans and guinea pigs do not. Despite this difference, rats and mice were selected for this study because: 1) the have been used extensively in previous carcinogenesis bioassays and are the subjects of a large historical data base; 2) they have a shorter life span than guinea pigs; and 3) they produce much less ascorbic acid than the amounts administered in this study. Unstressed rats have been reported to produce about 40 mg/kg/day, whereas the high-dose rats in this study ingested approximately 2,600 mg per day.

High-dose rats and mice in the 2-year study were fed diets containing L-ascorbic acid at the highest dietary concentration recommended (50,000 ppm) by the guidelines of the Bioassay Program. There was a mild sex difference in both rats and mice in relation to weight gain and survival. Survival of dosed and control female rats and of dosed and control female mice were comparable. Survival of high-dose male rats was slightly longer (P=0.087) than that of controls, and the result of the trend test for survival over all groups of male rats was marginally significant (P=0.057). High-dose male mice had significantly (P=0.009) longer survival than the controls, and the result of the trend test for survival over all groups of male mice was statistically significant (P=0.005). Throughout most of the study, mean body weights of dosed female rats and female mice were lower than those of the controls.

In the 13-week study, reticulum-cell hyperplasia was observed in 2/10 female rats receiving 25,000 ppm, 1/10 female rats receiving 50,000 ppm, and 4/10 receiving 100,000 ppm. In the 2-year study, the reticulum cell hyperplasia was seen in only 1/49 female rats in the 50,000 ppm group. The reason for this difference is not known.

The incidence of low-dose female rats with mononuclear cell (or undifferentiated) leukemias was statistically significant ($P<0.02$; control, 6/50, 12%; low-dose, 17/50, 34%; high-dose, 12/50, 24%). Since the incidence in the high-dose group was not significantly ($P>0.07$) higher than that in the controls, since the trend was not significant ($P\geq0.07$), and since no increases were observed for male rats, the increased incidence in the low-dose group was considered not to be related to administration of L-ascorbic acid. The historical incidence of untreated control female F344/N rats with leukemias is 49/288 (17.0%) for the same laboratory and 443/3758 (11.8%) throughout the Bioassay Program (Appendix H, Table H1).

A statistically significant ($P<0.05$) negative trend occurred in the incidence of female mice with lymphocytic leukemia (control, 3/50; low-dose, 0/50; high-dose, 0/50). Because the incidence of females with all types of leukemia or with either malignant lymphomas or leukemia was not statistically significant, the lower incidence of lymphocytic leukemia in the dosed females was not considered to be related to administration of L-ascorbic acid. Significant negative trends ($P<0.05$, life table) were observed in the incidences of male mice with malignant lymphocytic lymphoma, all malignant lymphomas, and combined lymphomas or leukemia (control, 9/50, 18%; low-dose, 8/50, 16%; high-dose, 3/50, 6%). The incidence of high-dose males with either lymphomas or leukemia was significantly lower than that in the controls. The incidences of male mice with lymphomas or with either lymphomas or leukemia was within the range of incidences of these tumors in groups of 35 or more untreated control male $B6C3F_1$ mice in the Bioassay Program. Thus, as in the female $B6C3F_1$ mice, the lower incidence of lymphomas or leukemia in the dosed groups is not considered to be related to administration of L-ascorbic acid.

The increased incidence of low-dose male mice with hemangiosarcomas was statistically significant (P=0.047; control, 1/50, 2%; low-dose, 4/50, 8%; high-dose, 0/50). This lesion was not seen at significant incidences in other dosed groups of rats or mice, and this low-dose effect was considered not to be related to administration of L-ascorbic acid. The hemangiosarcomas were detected in bone marrow, liver, and spleen. The historical incidence of hemangiosarcomas in untreated control male $B6C3F_1$ mice at this laboratory is 4/348 (1.1%) (Appendix H, Table H4).

A decrease in adenomas (alone) of the pituitary gland was seen for female rats: control, 25/50; low-dose, 19/50; high-dose, 15/50. The trend tests ($P<0.04$) and the high dose versus control incidence comparisons ($P<0.05$) confirmed the decreases observed in dosed groups. Except for the incidental tumor trend test ($P<0.05$), the other tests of association disappear when adenomas or carcinomas of the pituitary gland are combined and these rates are compared (26/50, 20/50, 18/50).

Since the progression from adenoma to carcinoma represents stages in the continuum of benignity to malignancy, the combined incidence rates are most appropriate for evaluation. Thus, this isolated decrease is not considered related to the administration of L-ascorbic acid because the combined incidence rates are biologically not different, and because these decreases were not seen in male rats or in male or female mice.

Adenocarcinomas occurred in the preputial gland of male rats and in the clitoral gland of female rats with significant ($P<0.05$, life table) negative trends (males: control, 3/50, 6%; low-dose, 1/50, 2%; high-dose, 0/50; females: control, 3/50, 6%; low-dose, 0/50; high-dose, 0/50). The incidences in the controls were higher than those previously observed in untreated F344/N rats at this laboratory (males: 5/290, 1.7%; females: 4/288, 1.4%) and the incidences in all dosed groups were within the range of incidences observed in groups of 35 or more untreated F344/N rats in the Bioassay Program (Appendix H, Tables H2 and H3), and thus these marginally lower incidences in the dosed groups are not considered to be related to the administration of L-ascorbic acid.

The incidence of male mice with hepatocellular carcinomas occurred with a significant ($P<0.05$, life table) negative trend (control, 10/50, 20%; low-dose, 12/49, 24%; high-dose, 4/50, 8%) and the incidence in the high-dose group was significantly lower than that in the controls ($P<0.05$, life table). No significant differences in the incidence of male or female mice with either hepatocellular adenomas or carcinomas were found by any of the tests used. Because the incidence of male mice with hepatocellular carcinomas in the concurrent control group is considerably higher than the historical control incidence and because the incidence in the high-dose group is virtually the same as the historical control rate observed at this laboratory (30/347, 8.6%; see Appendix H, Table H5), this reduction in carcinomas alone for male mice is not considered to be related to administration of L-ascorbic acid.

In female rats, myocardial degeneration, nephropathy, and osteopetrosis of the femur showed a significant dose related decline (Table 18). These all represent common degenerative lesions of the aging rat. While it seems reasonable to relate the decrease of degenerative changes to ascorbic acid exposure, similar changes were not found in the male rats. Further, there were no effects on degenerative lesions in the mice of either sex. Thus, the significance of the findings in female rats is uncertain.

These borderline increases and decreases in neoplastic lesions, as well as the decrease in nonneoplastic effects in female rats, were considered to be insufficient evidence for a compound-related effect.

Conclusions: Under the conditions of this bioassay, L-ascorbic acid was not carcinogenic for male and female F344/N rats or male and female B6C3F$_1$ mice.

TABLE 18. COMPARISON OF INCIDENCES OF NONNEOPLASTIC LESIONS IN THE L-ASCORBIC ACID STUDY *(a)*

Lesion	Dose (Percent in diet) 0	2.5	5.0
Male Rats			
Adrenal Cortex: Lipoidosis	5/49 (10%) P=0.027N *(b)*	4/50 (8%) NS	0/50 (0%) P=0.027N
Female Rats			
Heart Myocardium: Degeneration	43/50 (86%) P=0.007N	29/50 (58%) P=0.002N	31/50 (62%) P=0.006N
Liver: Chronic Focal Inflammation	8/50 (16%) P<0.001N	1/50 (2%) P=0.015N	0/50 (0%) P=0.003N
Kidney: Nephropathy	25/50 (50%) P=0.015N	10/50 (20%) P=0.002N	14/49 (29%) P=0.024N
Adrenal Cortex: Hyperplasia	12/50 (24%) P=0.003N	7/50 (14%) NS	2/49 (4%) P=0.004N
Thyroid: C-Cell Hyperplasia	28/49 (57%) P=0.016N	19/50 (38%) P=0.044N	17/49 (35%) P=0.021N
Osteopetrosis	27/50 (54%) P<0.001N	20/50 (40%) NS	10/50 (20%) P<0.001N
Male Mice			
Kidney/Tubule: Regeneration	21/50 (42%) NS	6/49 (12%) P<0.001N	28/50 (56%) NS
Female Mice			
Kidney/Tubule: Regeneration	6/49 (12%) P=0.016N	0/49 (0%) P=0.013N	1/50 (2%) P=0.053N

(a) Statistics provided are: Under Dose (Percent in Diet) 0% — Trend analysis (Cochran-Armitage test).
Under Dose (Percent in Diet) 2.5% — Low dose vs. Control (Fisher's exact test).
Under Dose (Percent in Diet) 5.0% — High dose vs. Control (Fisher's exact test).
NS — Not statistically significant

(b) A negative trend or lower incidence is indicated by N.

V. REFERENCES

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AMA, AMA Drug Evaluations; 1980:827.

Ames Co., Operating manual hema-tek slide staining pak. Elkhart, Indiana: Ames Co., Division of Miles Laboratories; 1974.

Armitage, P., Statistical methods in medical research. New York: John Wiley & Sons, Inc.; 1971:362-365.

Ashwell, G.; Kanfer, J; Smiley, J.; Burns, J., Metabolism of ascorbic acid and related uronic acids, aldonic acids, and pentoses. Ann. N.Y. Acad. Sci. 92:105-113; 1961.

Banic, S., Vitamin C acts as a cocarcinogen to methyl cholanthrene in guinea-pigs. Cancer Letters 11:239-242; 1981.

Berenblum, I., ed., Carcinogenicity testing: a report of the panel on carcinogenicity of the cancer research commission of UICC. Geneva: International Union Against Cancer, Vol. 2, 1969.

Bhatavdekar, J.; Shah, V., The effect of x-ray radiation on ascorbic acid content of some endocrine tissues of guinea pig, rat, and mouse. Acta Histochem. Cytochem. 13(3):270-276; 1980.

Blaschke, E.; Hertting, G., Enzymic methylation of L-ascorbic acid by catechol o-methyltransferase. Biochem. Pharmacol. 20:1363-1370; 1971.

Burns, J.; Mosbach, E.; Schulenberg, S., Ascorbic acid synthesis in normal and drug-treated rats studied with L-ascorbic-1-C^{14} acid. J. Biol. Chem. 207:679; 1954.

Calabrese, E., Nutrition and environmental health: the influence of nutritional status on pollutant toxicity and carcinogenicity, Volume 1: the vitamins. New York: John Wiley & Sons, Inc.; 1980.

Cameron, E.; Pauling, L., Cancer and vitamin C. The Linus Pauling Institute of Science and Medicine; 1979

Chauhan, P.; Aravindakshan, M.; Sundaram, K., Evaluation of ascorbic acid for mutagenicity by dominant lethal test in male Wistar rats. Mut. Res. 53:166-167; 1978.

CFR, U.S. Code of Federal Regulations 21:121.101; 1974.

Conney, A.; Bray, G.; Evans, C.; Burns, J., Metabolic interactions between L-ascorbic acid and drugs. Ann. N.Y. Acad. Sci. 92:115-127; 1961.

Cox, D., Regression models and life tables. J. R. Stat. Soc. BB34:187-220; 1972.

Curtin, C.; King. C., The metabolism of ascorbic acid-1-C^{14} and oxalic acid - C^{14} in the rat. J. Biol. Chem. 216:539-548; 1955.

Demole, V., On the physiological action of ascorbic acid and some related compounds. Biochem. J. 28:770-773; 1934.

El-Bana, M.; Hani-Ayobe, M.; Malak; Saleh, A.; El-Damarawy, N., Studies on the metabolic effects of L-ascorbic acid. Ain Shams Med. J. 29(1-2):57-60; 1978.

Frith, C.; Rule, J.; Kodel, R., The effect of ascorbic acid on the induction of urothelial lesions in mice by 2-acetylaminofluorene. Toxicol. Lett. 6:309-318; 1980.

Gart, J.; Chu, K.; Tarone, R., Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62(4):957; 1979.

Gilman, A.; Goodman, L.; Gilman, A., ed., Goodman and Gilman's the pharmacological basis of therapeutics, 6th ed., New York: MacMillan Publishing Co., Inc., 1980: 1576.

Heddle, J.; Bruce, W., Comparison of tests for mutagenicity or carcinogenicity using assays for sperm abnormalities, formation of micronuclei, and mutations in *Salmonella.* Cold Spring Harbor Conf. Cell Proliferation, 4c:1549-1557; 1977.

Hewitt, C.; Dickes, G., Biochem. J. 78:384; 1961.

Hornig, D., Distribution of ascorbic acid, metabolites and analogues in man and animals. Ann. N.Y. Acad. Sci. 258:103-118; 1975.

Irwin, M.; Hutchins, B., A conspectus of research on vitamin C requirements of man. J. Nutr. 106: 823-879; 1976.

Ito, N., Effects of promoters on n-butyl-n-(4-hydroxybutyl nitrosamine induced bladder carcinogenesis in the rat. In Abstracts: internat. symp. on health effects and tumor promotion; Oct. 12-15, 1981.

Kanfer, J.; Ashwell, G.; Burns, J., Formation of L-lyxonic and L-xylonic acids from L-ascorbic acid in rat kidney. J. Biol. Chem. 235:2518-2521; 1960.

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

V. REFERENCES

Kirk-Othmer, Encyclopedia of chemical technology, 2nd ed. New York: Interscience Publishers, Vol. 2:747-762; 1963; Vol. 4:342-344; 1964.

Kirk-Othmer, Encyclopedia of chemical technology, 3rd ed. New York: Interscience Publishers, Vol. 4:715-716; 1978.

Klaui, H., in Birch, G.; Parker, K; eds, Vitamin C: Recent aspects of its physiological and technological importance. New York: John Wiley and Sons, Inc.; 1974:16-30.

Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J., Carcinogenesis bioassay data system. Comp. Biomed. Res. 7:230-248; 1974.

Lynch, M. J.; Rapheal, S. S.; Mellor, L. D.; Spare, P. D.; Inwood, M. J. H., Medical laboratory technology and clinical pathology, 2nd ed. Philadelphia: W. B. Saunders Co.; 1969.

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

Maronpot, R.R.; Boorman, G.A., Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Toxicol. Pathol.; in press.

Marcusen, D.; Heninger, R., Effect of ascorbic acid on the pituitary-thyroid system in the rat. J. Endocr. 70:313-314; 1976.

Merck index, 9th ed., Rahway, NJ; Merck and Co., 1976:845.

Miale, G. B., Laboratory medicine hematology, 3rd ed. St. Louis: The C. V. Mosby Co.; 1967.

Miller, R. G., Jr., Simultaneous statistical inference, New York: McGraw-Hill Book Co., 1966.

Mumma, R.; Verlangieri, A., Isolation of ascorbic acid 2-sulfate from selected rat organs. Biochem. Biophys. Acta 273:249-253; 1972.

Murad, S.; Grove, D.; Lindberg, K. A.; Reynolds, G.; Sivarajah, S.; Pinnell, S. K., Proc. Natl. Acad. Sci. 78:2879-2882; 1981.

Nandi, B.; Majumder, A.; Subramanian, N.; Chatterjee, I., Effects of large doses of vitamin C in guinea pigs and rats. J. Nutrition 103(12):1688-1695; 1973.

National Academy of Sciences, Histologic typing of liver tumors of the rat. J. Natl. Cancer Inst. 64:179; 1980.

Omura, H.; Shinohara, K.; Maeda, H.; Nonaka, M.; Murakami, H., Mutagenic action of triose reductone and ascorbic acid on *Salmonella typhimurium* AT (sic) 100 strain. J. Nutr. Sci. Vitaminology 24:185-194; 1978.

Pauling, L., Evolution and the need for ascorbic acid. Proc. Nat. Acad. Sci. 67(4):1643-1648; 1970.

Peto, R.; Pike, M.; Day, N.; Gray, R.; Lee, P.; Parish, S.; Peto, J.; Richard, S.; Wahrendorf, J., Guidelines for simple sensitive, significant tests for carcinogenic effects in long-term animal experiments. International Agency for Research Against Cancer. Monographs on the long-term and short-term screening assays for carcinogens: A critical appraisal. Geneva: World Health Organization. Supplement 2; 1980:311.

Rosin, M.; Richard, H; Stich, H., Mutagenic activity of ascorbate in mammalian cell cultures. Cancer Letters 8:299-305; 1980.

Sadtler standard spectra, Philadelphia: Sadtler Research Laboratories, IR Nos. 5424 and 13217; NMR No. 3126M.

Salomon, L.; Stubbs, D., Some aspects of the metabolism of ascorbic acid in rats. Ann. N.Y. Acad. Sci. 92:128-140; 1961.

Speit, G.; Wolf, M.; Vogel, W., The SCE-inducing capacity of vitamin C: investigations in vitro and in vivo. Mutat. Res. 78:273-278; 1980.

Squire, R.; Levitt, M., Report of a workshop on classification of specific hepatocellular lesions in rats. Cancer Res. 35:3214; 1975.

Stich, H. F.; Karim, J.; Koropatnick, J.; Lo, L., Mutagenic action of ascorbic acid. Nature 260:722; 1976.

Stich, H.; Wei, L.; Lam, P., The need for a mammalian test system for mutagens: action of some reducing agents. Cancer Letters 5:199-204; 1978.

Stich, H. F.; Wei, L.; Whiting, R. F., Chromosome aberrations in mammalian cells exposed to vitamin C and mulitple vitamin pills. Food Cosmet. Toxicol. 18:497; 1980.

Stone, I., Humans, the mammalian mutants. Amer. Lab. 6(4):32-39; 1974.

Surber, W.; Cerioli, A., 1971, cited in WHO Food Additive Series No. 5, Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. 1974:143-145.

Takenouchi, K.; Aso, K.; Kawase, K.; Ichikawa, H.; Shiomi, T., On the metabolites of ascorbic acid, especially oxalic acid, eliminated in urine, following the administration of large amounts of ascorbic acid. J. Vitaminology 12:49-58; 1966.

V. REFERENCES

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

Tolbert, B.; Downing, M.; Carlson, R.; Knight, M.; Baker, E., Chemistry and metabolism of ascorbic acid and ascorbate sulfate. Ann. N.Y. Acad. Sci. 258:48-69; 1975.

United States Pharmacopeia, XIX, U.S. Pharmacopeial Convention, Inc., Rockville, Maryland, 1975:36-39.

USITC, United States International Trade Commission, Synthetic Organic Chemicals, United States Production and Sales 1980, USITC Publication 1183, U.S. Government Printing Office, Washington, D.C.; 1981.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED DIETS CONTAINING L-ASCORBIC ACID

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED DIETS CONTAINING L-ASCORBIC ACID

	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)
BASAL-CELL CARCINOMA	2 (4%)		
FIBROSARCOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
TRICHOEPITHELIOMA		1 (2%)	
FIBROMA	1 (2%)	1 (2%)	1 (2%)
FIBROSARCOMA	1 (2%)		
LIPOMA			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEAL MUSCLE	(49)	(49)	(47)
FOLLICULAR-CELL CARCINOMA, INVAS			1 (2%)
#LUNG	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA			2 (4%)
OSTEOSARCOMA	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	1 (2%)	
UNDIFFERENTIATED LEUKEMIA	16 (32%)	16 (32%)	14 (28%)
#SPLEEN	(48)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
UNDIFFERENTIATED LEUKEMIA	1 (2%)		
#MESENTERIC L. NODE	(45)	(42)	(48)
LEIOMYOSARCOMA, METASTATIC		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(40)	(43)	(42)
ALVEOLAR/BRONCHIOLAR CA, INVASIV			1 (2%)
THYMOMA, MALIGNANT			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV	1 (2%)		
#LIVER	(49)	(50)	(50)
NEOPLASTIC NODULE	1 (2%)		
HEPATOCELLULAR CARCINOMA	1 (2%)		1 (2%)
#STOMACH	(49)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
#SMALL INTESTINE	(49)	(49)	(48)
LEIOMYOSARCOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	
#KIDNEY/PELVIS	(49)	(50)	(50)
TRANSITIONAL-CELL PAPILLOMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(45)	(50)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS	9 (19%)	9 (20%)	14 (28%)
ADENOCARCINOMA, NOS			1 (2%)
CHROMOPHOBE ADENOMA	1 (2%)		
CHROMOPHOBE CARCINOMA	1 (2%)		
#ADRENAL	(49)	(50)	(50)
PHEOCHROMOCYTOMA	8 (16%)	10 (20%)	14 (28%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(49)	(50)	(50)
FOLLICULAR-CELL CARCINOMA	1 (2%)		2 (4%)
C-CELL ADENOMA	2 (4%)	4 (8%)	6 (12%)
C-CELL CARCINOMA	4 (8%)	2 (4%)	2 (4%)
#PARATHYROID	(37)	(42)	(40)
ADENOMA, NOS		1 (2%)	1 (3%)
#PANCREATIC ISLETS	(49)	(50)	(49)
ISLET-CELL ADENOMA			1 (2%)
ISLET-CELL CARCINOMA	2 (4%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA	2 (4%)	2 (4%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	3 (6%)	1 (2%)	
#TESTIS	(50)	(50)	(49)
INTERSTITIAL-CELL TUMOR	48 (96%)	49 (98%)	46 (94%)
MESOTHELIOMA, MALIGNANT		1 (2%)	
NERVOUS SYSTEM			
#CEREBRUM	(49)	(50)	(49)
ASTROCYTOMA			1 (2%)
#BRAIN	(49)	(50)	(49)
FIBROSARCOMA		1 (2%)	
#CEREBELLUM	(49)	(50)	(49)
MENINGIOMA	1 (2%)		
SPECIAL SENSE ORGANS			
*EAR	(50)	(50)	(50)
LEIOMYOSARCOMA			1 (2%)
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CARCINOSARCOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF THORAX	(50)	(50)	(50)
FIBROMA			1 (2%)
BODY CAVITIES			
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
FIBROSARCOMA, METASTATIC	1 (2%)		
MESOTHELIOMA, MALIGNANT		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	4	6	3
MORIBUND SACRIFICE	13	9	6
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	33	35	41
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	50	50	50
TOTAL PRIMARY TUMORS	113	103	114
TOTAL ANIMALS WITH BENIGN TUMORS	48	49	48
TOTAL BENIGN TUMORS	72	77	86
TOTAL ANIMALS WITH MALIGNANT TUMORS	30	24	24
TOTAL MALIGNANT TUMORS	39	26	28
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	1	2
TOTAL SECONDARY TUMORS	3	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2		
TOTAL UNCERTAIN TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED DIETS CONTAINING L-ASCORBIC ACID

	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			
*SUBCUT TISSUE	(50)	(50)	(50)
BASAL-CELL CARCINOMA	1 (2%)		
FIBROMA	1 (2%)	2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		
OSTEOSARCOMA, METASTATIC	2 (4%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
UNDIFFERENTIATED LEUKEMIA	5 (10%)	17 (34%)	12 (24%)
#SPLEEN	(50)	(50)	(49)
UNDIFFERENTIATED LEUKEMIA	1 (2%)		
#THYMUS	(47)	(43)	(40)
SQUAMOUS CELL CARCINOMA			1 (3%)
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(49)
HEMANGIOSARCOMA	1 (2%)		
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	2 (4%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)	2 (4%)	3 (6%)
ADENOMA, NOS	24 (48%)	19 (38%)	15 (30%)
CHROMOPHOBE ADENOMA	1 (2%)		
GLIOMA, NOS	1 (2%)		
#PITUICYTE	(50)	(50)	(50)
GLIOMA, NOS	1 (2%)		
#ADRENAL	(50)	(50)	(49)
CORTICAL ADENOMA	3 (6%)	2 (4%)	1 (2%)
CORTICAL CARCINOMA	1 (2%)		
PHEOCHROMOCYTOMA	4 (8%)	6 (12%)	7 (14%)
#THYROID	(49)	(50)	(49)
FOLLICULAR-CELL CARCINOMA	1 (2%)	1 (2%)	
C-CELL ADENOMA	2 (4%)	6 (12%)	4 (8%)
C-CELL CARCINOMA		1 (2%)	1 (2%)
#THYROID FOLLICLE	(49)	(50)	(49)
PAPILLARY ADENOMA	1 (2%)		
#PANCREATIC ISLETS	(49)	(50)	(48)
ISLET-CELL ADENOMA	1 (2%)		
ISLET-CELL CARCINOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)	1 (2%)
ADENOCARCINOMA, NOS	1 (2%)		1 (2%)
FIBROADENOMA	5 (10%)	6 (12%)	8 (16%)
*CLITORAL GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	3 (6%)		
#UTERUS	(50)	(50)	(50)
CARCINOMA-IN-SITU, NOS	1 (2%)		
LEIOMYOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	13 (26%)	9 (18%)	13 (26%)
ENDOMETRIAL STROMAL SARCOMA		1 (2%)	1 (2%)
#CERVIX UTERI	(50)	(50)	(50)
FIBROMA			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
PAPILLOMA, NOS			1 (2%)
PAPILLARY CARCINOMA		1 (2%)	
ADENOCARCINOMA, NOS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE		1 (2%)	1 (2%)
OLIGODENDROGLIOMA	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
*ZYMBAL'S GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(50)
FIBROMA			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
LEG			
OSTEOSARCOMA	1		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	3	2	3
MORIBUND SACRIFICE	9	12	10
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	38	36	37
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	41	45	40
TOTAL PRIMARY TUMORS	85	78	71
TOTAL ANIMALS WITH BENIGN TUMORS	36	37	33
TOTAL BENIGN TUMORS	56	52	52
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	25	17
TOTAL MALIGNANT TUMORS	27	26	19
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	1
TOTAL SECONDARY TUMORS	2	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2		
TOTAL UNCERTAIN TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	102	105	101	105	059	105	103	105	080	101	093	093	085	101	105	105	105	105	105	105	101	095
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA										X															
FIBROSARCOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA					X																				
FIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																X									
OSTEOSARCOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+
UNDIFFERENTIATED LEUKEMIA																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	-	+	+	-	+	+
THYMUS	+	+	-	+	+	+	+	+	+	+	+	-	+	-	+	+	+	-	-	-	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE																									
LIVER	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE													X												
HEPATOCELLULAR CARCINOMA						X																			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	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
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
KIDNEY/PELVIS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA			X																						
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS													X												
ADENOMA, NOS																		X	X						
CHROMOPHOBE ADENOMA																									
CHROMOPHOBE CARCINOMA																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA	X	X		X		X							X		X										
THYROID	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA											X														
C-CELL ADENOMA			X																			X			
C-CELL CARCINOMA																									
PARATHYROID	+	+	-	+	+	+	+	+	+	+	-	-	+	+	-	-	+	-	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL CARCINOMA		X	X																						
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	N	N	N	N	+	N	N	+	N	N	+	+	N	+	N	+	+	+	N	+	N	+	N
FIBROADENOMA										X															
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL 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
ADENOCARCINOMA, NOS													X												
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
MENINGIOMA																									
SPECIAL SENSE ORGANS																									
ZYMBAL'S 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
SQUAMOUS CELL CARCINOMA																X									
CARCINOSARCOMA																									
BODY CAVITIES																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS																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
FIBROSARCOMA, METASTATIC								X																	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
UNDIFFERENTIATED LEUKEMIA			X	X		X					X			X	X				X						X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	091	074	072	105	070	105	105	105	105	086	105	105	085	105	105	097	101	047	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	50M
BASAL-CELL CARCINOMA					X																X					2
FIBROSARCOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	50M
FIBROMA																										1
FIBROSARCOMA			X																							1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA, METASTAT																										1
OSTEOSARCOMA													X													1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
UNDIFFERENTIATED LEUKEMIA		X																								1
LYMPH NODES	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
THYMUS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SQUAMOUS CELL CARCINOMA, INVASIVE						X																				1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NEOPLASTIC NODULE																										1
HEPATOCELLULAR CARCINOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	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	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	45
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
KIDNEY/PELVIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
TRANSITIONAL-CELL PAPILLOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CARCINOMA,NOS																							X			1
ADENOMA, NOS		X	X		X		X																	X	X	9
CHROMOPHOBE ADENOMA												X														1
CHROMOPHOBE CARCINOMA														X												1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA												X							X							8
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL CARCINOMA																										1
C-CELL ADENOMA							X																		X	2
C-CELL CARCINOMA	X																								X	4
PARATHYROID	-	+	+	-	-	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+	-	+	+	+	+	37
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL CARCINOMA																										2
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	N	+	N	+	+	+	N	N	+	N	+	N	N	+	N	+	N	N	+	+	+	50M
FIBROADENOMA													X													2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	48
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PREPUTIAL/CLITORAL 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	50M
ADENOCARCINOMA, NOS		X																			X					3
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MENINGIOMA				X																						1
SPECIAL SENSE ORGANS																										
ZYMBAL'S 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	50M
SQUAMOUS CELL CARCINOMA						X																				1
CARCINOSARCOMA																										1
BODY CAVITIES																										
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
MESOTHELIOMA, NOS																										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	50M
FIBROSARCOMA, METASTATIC																					X					1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
UNDIFFERENTIATED LEUKEMIA	X			X							X		X			X			X	X	X					16

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	104	105	105	097	105	105	102	103	105	082	105	105	105	105	105	074	101	105	105	105	105	085	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
TRICHOEPITHELIOMA																									
FIBROMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+
LEIOMYOSARCOMA, METASTATIC											X														
THYMUS	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	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
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA											X														
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOCARCINOMA																				X					
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
ADENOMA, NOS	X						X						X	X	X										
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA		X		X		X	X					X												X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA			X																						
C-CELL CARCINOMA			X															X							
PARATHYROID	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+
ADENOMA, NOS			X																						
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	+	N	+	+	N	+	N	N	+	+	+	+	+	+	N	+	N	N	N	N	N
FIBROADENOMA																									
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MESOTHELIOMA, MALIGNANT																	X								
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL 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
ADENOCARCINOMA, NOS																	X								
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																							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, MALIGNANT					X																				
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
UNDIFFERENTIATED LEUKEMIA		X				X		X		X		X						X	X	X					X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	0246	0247	0248	0249	0310	0312	0320	0331	0345	0355	0356	0357	0358	0359	0401	0411	0422	0431	0441	0445	0456	0467	0481	0495	0501	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	057	055	055	055	089	115	097	055	055	055	055	053	055	080	055	055	055	051	087	055	097	095	105	051	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	50M
TRICHOEPITHELIOMA								X																		1
FIBROMA																			X							1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	-	+	+	-	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	42
LEIOMYOSARCOMA, METASTATIC																										1
THYMUS	+	-	+	+	+	+	+	+	+	+	•	+	+	-	+	+	+	+	+	-	+	+	+	-	•	43
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	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	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
LEIOMYOSARCOMA																										1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOCARCINOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
ENDOCRINE SYSTEM																										
PITUITARY	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	45
ADENOMA, NOS							X									X	X							X		9
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA							X				X							X			X					10
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA													X	X										X		4
C-CELL CARCINOMA																										2
PARATHYROID	-	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	42
ADENOMA, NOS																										1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL CARCINOMA																				X						1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	N	+	N	N	+	N	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	N	50M
FIBROADENOMA						X												X								2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	49
MESOTHELIOMA, MALIGNANT																										1
PROSTATE	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	50
PREPUTIAL/CLITORAL 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	50M
ADENOCARCINOMA, NOS																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROSARCOMA																										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	50M
MESOTHELIOMA, MALIGNANT																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE									X																	1
UNDIFFERENTIATED LEUKEMIA		X		X									X		X	X							X		X	16

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	090	105	080	105	105	098	105	105	105	095	105	105	105	105	105	105	105	064	101	105	105	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																					X				
LIPOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA													X												
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA, INVASI						X																			
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	-	-	+	+	+	-	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CA, INVASIVE													X												
THYMOMA, MALIGNANT																									
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA																							X		
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	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
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																				X					
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS					X	X						X		X				X			X		X	X	
ADENOCARCINOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA		X				X	X	X			X			X								X		X	X
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA						X																			
C-CELL ADENOMA																	X	X					X		X
C-CELL CARCINOMA																									
PARATHYROID	+	+	-	+	+	+	-	+	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS		X																							
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ISLET-CELL ADENOMA																							X		
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	N	N	N	+	+	+	+	+	+	+	N	N	+	N	N	N	+	+	N	N	N
FIBROADENOMA																									
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	
ASTROCYTOMA																									
SPECIAL SENSE ORGANS																									
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+
LEIOMYOSARCOMA																									X
MUSCULOSKELETAL SYSTEM																									
MUSCLE	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
FIBROMA																									
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
UNDIFFERENTIATED LEUKEMIA		X	X					X	X					X											

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	100	105	105	105	105	105	105	074	105	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROMA																										1
LIPOMA							X																			1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA																								X		2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
FOLLICULAR-CELL CARCINOMA, INVASI																										1
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, HISTIOCYTIC TYPE							X																			1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYMUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	42
ALVEOLAR/BRONCHIOLAR CA, INVASIVE																										1
THYMOMA, MALIGNANT								X																		1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	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	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS		X										X	X				X		X	X						14
ADENOCARCINOMA, NOS																					X					1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA		X	X														X		X					X		14
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA																										2
C-CELL ADENOMA										X			X						X							6
C-CELL CARCINOMA		X			X																					2
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	-	+	-	40
ADENOMA, NOS																										1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																	X									1
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	N	+	+	+	+	N	N	N	+	+	+	+	+	+	N	+	+	+	+	+	+	N	N	50M
FIBROADENOMA					X																					1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X			X	X	X	X	X	X	X	46
PROSTATE	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+		47
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ASTROCYTOMA										X																1
SPECIAL SENSE ORGANS																										
EAR	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	50M
LEIOMYOSARCOMA																										1
MUSCULOSKELETAL SYSTEM																										
MUSCLE	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	50M
FIBROMA					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	50M
UNDIFFERENTIATED LEUKEMIA	X	X	X							X	X	X	X		X						X				X	14

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

CONTROL

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	083	082	105	105	105	105	105	105	105	088	105	093	105	093	105	097	097	105	105	105	105	105	105	105	089
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
BASAL-CELL CARCINOMA																			X						
FIBROMA					X																				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA														X											
OSTEOSARCOMA, METASTATIC					X	X																			
TRACHEA	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA	X																								
UNDIFFERENTIATED LEUKEMIA																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE								X																	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	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
PANCREAS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS			X	X			X	X	X		X			X			X			X	X				
CHROMOPHOBE ADENOMA												X													
GLIOMA, NOS																			X						
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
CORTICAL CARCINOMA																									
PHEOCHROMOCYTOMA				X							X														
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY ADENOMA								X																	
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA				X																					
PARATHYROID	+	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	-	+	-	+	+	+	-
PANCREATIC ISLETS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																				X					
ISLET-CELL CARCINOMA				X																					
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	N	+	+	+
ADENOCARCINOMA, NOS																									
FIBROADENOMA																	X			X					X
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N
ADENOCARCINOMA, NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA-IN-SITU, NOS																									
ADENOCARCINOMA, NOS																									
ENDOMETRIAL STROMAL POLYP	X					X					X		X								X		X		
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OLIGODENDROGLIOMA																									
SPECIAL SENSE ORGANS																									
LACRIMAL 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																									
ZYMBAL'S 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			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															
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																X									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
UNDIFFERENTIATED LEUKEMIA								X				X													
LEG NOS																									
OSTEOSARCOMA					X																				

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	063	105	080	105	105	105	105	080	105	105	105	105	105	088	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
BASAL-CELL CARCINOMA																										1
FIBROMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
OSTEOSARCOMA, METASTATIC																										2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA					X																					1
UNDIFFERENTIATED LEUKEMIA																										1
LYMPH NODES	-	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	+	-	+	+	-	+	+	+	42
THYMUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE		X																								2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	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	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																							X			1
ADENOMA, NOS		X	X		X			X		X	X	X	X			X	X		X	X	X			X		24
CHROMOPHOBE ADENOMA																										1
GLIOMA, NOS													X													2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA				X	X																			X		3
CORTICAL CARCINOMA																	X									1
PHEOCHROMOCYTOMA					X	X																				4
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
PAPILLARY ADENOMA																										1
FOLLICULAR-CELL CARCINOMA			X																							1
C-CELL ADENOMA				X																						2
PARATHYROID	+	+	+	+	+	-	-	+	+	+	-	+	+	+	-	+	+	+	+	+	+	-	+	-	+	38
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																										1
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	N	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	N	+	+	N	+	+	50M
ADENOCARCINOMA, NOS											X															1
FIBROADENOMA				X	X																					5
PREPUTIAL/CLITORAL 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	50M
ADENOCARCINOMA, NOS								X													X					3
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA-IN-SITU, NOS																										1
ADENOCARCINOMA, NOS																										1
ENDOMETRIAL STROMAL POLYP	X		X									X			X			X	X		X					13
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
OLIGODENDROGLIOMA												X														1
SPECIAL SENSE ORGANS																										
LACRIMAL 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	50M
ADENOMA, NOS					X																					1
ZYMBAL'S 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	50M
ADENOCARCINOMA, NOS																										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	50M
MALIGNANT LYMPHOMA, NOS																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																		X								1
UNDIFFERENTIATED LEUKEMIA													X						X		X					5
LEG NOS																										
OSTEOSARCOMA																										1

M ANIMALS NECROPSIED
+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

LOW DOSE

ANIMAL NUMBER	00112	00123	00134	00145	00156	00167	00178	00189	00190	01101	01112	01123	01134	01145	01156	01167	01178	01189	01190	02201	02212	02223	02234	02245
WEEKS ON STUDY	105	105	099	105	105	105	105	089	105	105	101	098	105	098	093	101	079	099	105	103	105	105	105	105
INTEGUMENTARY SYSTEM																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
FIBROMA					X																			
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	-	-	+	+	+	+	+	-	+	-	-	+	+	+	+	+	-	+	+	-	+	+
THYMUS	+	+	+	+	+	-	+	-	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	-
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA														X										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																			+					
ADENOMA, NOS		X	X				X		X	X			X					X	X	X	X		X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																								
PHEOCHROMOCYTOMA	X											X										X		
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA														X										
C-CELL ADENOMA													X								X	X		
C-CELL CARCINOMA										X														
PARATHYROID	+	+	+	-	+	+	+	-	-	+	-	+	+	+	+	-	-	+	+	+	-	+	+	+
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	N	+	+	+	+	+	+
ADENOMA, NOS															X							X		
FIBROADENOMA																								
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY CARCINOMA																								
LEIOMYOMA			X																					
ENDOMETRIAL STROMAL POLYP				X								X	X							X				
ENDOMETRIAL STROMAL SARCOMA																								
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, INVASIVE																								
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
MALIGNANT LYMPHOMA, NOS			X																					
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																								
UNDIFFERENTIATED LEUKEMIA		X						X			X	X		X	X	X							X	X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
$: ANIMAL MIS-SEXED
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	103	105	105	095	105	105	105	105	105	096	105	105	105	105	105	105	105	099	095	104	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA								X																		2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	40
THYMUS	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
ORAL CAVITY	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*
SQUAMOUS CELL CARCINOMA																										1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	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*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																					X					2
ADENOMA, NOS	X							X				X	X	X					X	X			X			19
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA			X											X												2
PHEOCHROMOCYTOMA				X						X		X														6
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA																										1
C-CELL ADENOMA														X					X				X			6
C-CELL CARCINOMA																										1
PARATHYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	40
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	50*
ADENOMA, NOS		X																								1
FIBROADENOMA							X	X								X								X		6
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PAPILLARY CARCINOMA	X																									1
LEIOMYOMA																										1
ENDOMETRIAL STROMAL POLYP			X		X				X								X			X						9
ENDOMETRIAL STROMAL SARCOMA											X															1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, INVASIVE																					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*
MALIGNANT LYMPHOMA, NOS																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE					X																					1
UNDIFFERENTIATED LEUKEMIA		X					X			X		X		X				X	X	X						17

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	115	102	103	105	072	094	105	105	105	105	105	091	105	105	105	104	105	105	105	072	105	105	086	105
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+	-	-	+
SQUAMOUS CELL CARCINOMA																									X
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	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
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS	X																X								
ADENOMA, NOS			X		X					X	X	X							X	X		X	X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA										X															
PHEOCHROMOCYTOMA				X															X						
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA													X												
C-CELL CARCINOMA																									
PARATHYROID	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+
ADENOMA, NOS							X										X	X			X				X
ADENOCARCINOMA, NOS																									
FIBROADENOMA																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS											X														
FIBROMA																									X
ENDOMETRIAL STROMAL POLYP		X	X		X										X	X		X				X		X	X
ENDOMETRIAL STROMAL SARCOMA																									
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, INVASIVE																	X								
MUSCULOSKELETAL SYSTEM																									
MUSCLE	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
FIBROMA					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
UNDIFFERENTIATED LEUKEMIA	X							X	X				X				X	X						X	

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	105	098	105	105	105	105	105	105	105	105	093	105	105	105	105	095	105	090	105	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	49
LYMPH NODES	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	A	+	-	+	44
THYMUS SQUAMOUS CELL CARCINOMA	-	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	-	+	+	+	A	+	+	+	40 1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	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	50M
PANCREAS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	49
URINARY BLADDER	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	45
ENDOCRINE SYSTEM																										
PITUITARY CARCINOMA,NOS ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+	50 3 15
		X				X											X					X	X		X	
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	49 1 7
		X					X		X											X					X	
THYROID C-CELL ADENOMA C-CELL CARCINOMA	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+	+	X	X	+	A	+	+	49 4 1
																									X	
PARATHYROID	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	43
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND ADENOMA, NOS ADENOCARCINOMA, NOS FIBROADENOMA	N	+	+	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	+	+	N	+	N	50M 1 1 8
		X	X							X						X								X		
UTERUS PAPILLOMA, NOS FIBROMA ENDOMETRIAL STROMAL POLYP ENDOMETRIAL STROMAL SARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1 1 13 1
		X		X				X													X					
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN CARCINOMA, NOS, INVASIVE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
MUSCULOSKELETAL SYSTEM																										
MUSCLE FIBROMA	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	50M 1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS UNDIFFERENTIATED LEUKEMIA	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	50M 12
					X		X				X							X	X							

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: *NO NECROPSY PERFORMED*

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE FED DIETS CONTAINING L-ASCORBIC ACID

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED DIETS CONTAINING L-ASCORBIC ACID

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROSARCOMA	1 (2%)	1 (2%)	
OSTEOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(49)
HEPATOCELLULAR CARCINOMA, METAST		4 (8%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	3 (6%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	5 (10%)
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (6%)	4 (8%)	3 (6%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	1 (2%)	
UNDIFFERENTIATED LEUKEMIA	1 (2%)		
EOSINOPHILIC LEUKEMIA		1 (2%)	
#SPLEEN	(50)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
#LYMPH NODE	(36)	(41)	(43)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE	1 (3%)		
CIRCULATORY SYSTEM			
#BONE MARROW	(48)	(49)	(50)
HEMANGIOSARCOMA		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(50)	(49)	(50)
HEMANGIOSARCOMA		2 (4%)	
#LIVER	(50)	(49)	(50)
HEMANGIOSARCOMA	1 (2%)	2 (4%)	
#PANCREAS	(49)	(48)	(50)
HEMANGIOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
HEPATOCELLULAR ADENOMA	6 (12%)	4 (8%)	9 (18%)
HEPATOCELLULAR CARCINOMA	10 (20%)	12 (24%)	4 (8%)
#CARDIAC STOMACH	(50)	(49)	(48)
SQUAMOUS CELL PAPILLOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY/CORTEX	(50)	(49)	(50)
ADENOMA, NOS			1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL	(50)	(49)	(49)
CORTICAL ADENOMA	2 (4%)	2 (4%)	
PHEOCHROMOCYTOMA		2 (4%)	
#THYROID	(48)	(44)	(49)
FOLLICULAR-CELL ADENOMA	1 (2%)		1 (2%)
#PANCREATIC ISLETS	(49)	(48)	(50)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
#TESTIS	(50)	(49)	(50)
INTERSTITIAL-CELL TUMOR		1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(50)	(49)	(50)
OSTEOSARCOMA, INVASIVE		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(50)	(50)
ADENOMA, NOS		3 (6%)	
*EAR	(50)	(50)	(50)
NEUROFIBROSARCOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	7	2
MORIBUND SACRIFICE	6	2	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	41	47
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	29	31	24
TOTAL PRIMARY TUMORS	36	44	29
TOTAL ANIMALS WITH BENIGN TUMORS	11	13	15
TOTAL BENIGN TUMORS	12	16	17
TOTAL ANIMALS WITH MALIGNANT TUMORS	21	24	11
TOTAL MALIGNANT TUMORS	24	28	12
TOTAL ANIMALS WITH SECONDARY TUMORS#		5	2
TOTAL SECONDARY TUMORS		6	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED DIETS CONTAINING L-ASCORBIC ACID

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
BASAL-CELL CARCINOMA	1 (2%)		
SARCOMA, NOS			2 (4%)
LEIOMYOSARCOMA	1 (2%)		
OSTEOSARCOMA	1 (2%)		
OSTEOSARCOMA, INVASIVE	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)	
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	5 (10%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	5 (10%)	3 (6%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	5 (10%)	3 (6%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	1 (2%)	1 (2%)
LYMPHOCYTIC LEUKEMIA	3 (6%)		
GRANULOCYTIC LEUKEMIA			1 (2%)
#MANDIBULAR L. NODE	(43)	(38)	(43)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
#BRONCHIAL LYMPH NODE	(43)	(38)	(43)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#MESENTERIC L. NODE	(43)	(38)	(43)
FIBROSARCOMA			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FIBROSARCOMA, INVASIVE			1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (5%)		
#RENAL LYMPH NODE	(43)	(38)	(43)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
#LIVER	(50)	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#PEYER'S PATCH	(49)	(46)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#KIDNEY	(49)	(49)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
#THYMUS	(36)	(37)	(39)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (3%)	
CIRCULATORY SYSTEM			
#BONE MARROW	(49)	(48)	(50)
HEMANGIOSARCOMA			1 (2%)
#SPLEEN	(50)	(48)	(50)
HEMANGIOSARCOMA	1 (2%)	1 (2%)	1 (2%)
*MUSCLE OF LEG	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(50)	(49)	(50)
HEMANGIOSARCOMA			1 (2%)
*MESENTERY	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
#UTERUS	(50)	(48)	(50)
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA			2 (4%)
#OVARY	(50)	(45)	(46)
HEMANGIOMA		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
HEPATOCELLULAR ADENOMA	2 (4%)	1 (2%)	2 (4%)
HEPATOCELLULAR CARCINOMA	1 (2%)		1 (2%)
HEPATOBLASTOMA	1 (2%)		
#CARDIAC STOMACH	(49)	(46)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#COLON	(50)	(49)	(49)
FIBROSARCOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(42)	(47)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS	2 (5%)		1 (2%)
CHROMOPHOBE ADENOMA		2 (5%)	
#ADRENAL	(50)	(48)	(50)
CORTICAL ADENOMA		1 (2%)	2 (4%)
PHEOCHROMOCYTOMA	2 (4%)	1 (2%)	
#THYROID	(44)	(44)	(43)
FOLLICULAR-CELL CARCINOMA	1 (2%)		
#PANCREATIC ISLETS	(49)	(46)	(49)
ISLET-CELL ADENOMA	1 (2%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ACINAR-CELL CARCINOMA	1 (2%)		1 (2%)
#UTERUS	(50)	(48)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
FIBROSARCOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP	3 (6%)	2 (4%)	
#OVARY	(50)	(45)	(46)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
GRANULOSA-CELL TUMOR	1 (2%)		
TERATOMA, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(50)
OSTEOSARCOMA, METASTATIC	1 (2%)		
*SPINAL CORD	(50)	(50)	(50)
OSTEOSARCOMA, INVASIVE	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS			1 (2%)
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SACRUM	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
*MEDIASTINUM	(50)	(50)	(50)
SARCOMA, NOS, INVASIVE		1 (2%)	
ALL OTHER SYSTEMS			
BASE OF TAIL			
SARCOMA, NOS			1
LEG			
LEIOMYOSARCOMA		1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	5	9	8
MORIBUND SACRIFICE	6	3	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	39	38	39
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	30	28	27
TOTAL PRIMARY TUMORS	40	31	40
TOTAL ANIMALS WITH BENIGN TUMORS	12	12	7
TOTAL BENIGN TUMORS	14	12	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	19	24
TOTAL MALIGNANT TUMORS	25	19	32
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	1
TOTAL SECONDARY TUMORS	4	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		1
TOTAL UNCERTAIN TUMORS	1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

CONTROL

ANIMAL NUMBER	0012	0021	0031	0041	0051	0061	0071	0081	0091	0101	0111	0121	0131	0141	0151	0161	0171	0181	0191	0201	0211	0221	0231	0241	0251
WEEKS ON STUDY	105	105	105	105	105	105	024	105	031	105	105	105	105	102	105	104	075	105	105	105	105	105	105	052	031	105
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA				X																						
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA						X																				
ALVEOLAR/BRONCHIOLAR CARCINOMA																	X									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										
LYMPH NODES	+	-	+	+	+	+	-	+	-	+	+	+	+	-	+	-	+	+	+	-	+	+	-	+	-
MALIGNANT LYMPHOMA, MIXED TYPE																	X									
THYMUS	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-	-	+	-	-	+	+	+	-	+	+
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA						X																X				X
HEPATOCELLULAR CARCINOMA	X													X											X	
HEMANGIOSARCOMA																										
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	N
PANCREAS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	-	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA										X	X															
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA													X													
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																										
EAR	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	N
NEUROFIBROSARCOMA		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	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	X																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																	X									
MALIGNANT LYMPHOMA, MIXED TYPE																										
UNDIFFERENTIATED LEUKEMIA																										

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	105	105	101	097	084	090	078	105	105	105	104	091	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	N	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	50*
FIBROSARCOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA				X																X					3
ALVEOLAR/BRONCHIOLAR CARCINOMA									X																2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE													X												1
LYMPH NODES	+	-	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	-	36
MALIGNANT LYMPHOMA, MIXED TYPE																									1
THYMUS	+	+	-	+	+	+	+	+	-	-	-	+	+	+	+	-	-	+	+	-	+	+	-	+	35
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA					X								X												6
HEPATOCELLULAR CARCINOMA	X		X				X				X	X								X	X				10
HEMANGIOSARCOMA							X																		1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	-	+	-	43
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																									2
THYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
FOLLICULAR-CELL ADENOMA																									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	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																									
EAR	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*
NEUROFIBROSARCOMA																									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	50*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE									X																2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE							X									X									3
MALIGNANT LYMPHOMA, MIXED TYPE					X																				1
UNDIFFERENTIATED LEUKEMIA															X										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: *NO NECROPSY PERFORMED*

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	079	105	105	105	077	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																									
OSTEOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA														X											
ALVEOLAR/BRONCHIOLAR ADENOMA		X																							
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
OSTEOSARCOMA, METASTATIC																									
TRACHEA	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	-	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA		X																							
LYMPH NODES	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	-	+	+	+	+	-	+	+	-	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
THYMUS	+	+	+	-	+	-	+	+	+	+	+	+	+	-	+	+	+	A	+	+	-	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA					X																				X
HEPATOCELLULAR CARCINOMA									X		X			X		X									
HEMANGIOSARCOMA			X																						
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	N	+	N	+	N	+	+	N	N	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
ESOPHAGUS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	-	+	-	+	+	+	+	+	-	-	+	+	+	-	A	-	+	+	+	-	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA													X												
PHEOCHROMOCYTOMA														X											
THYROID	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
PARATHYROID	+	-	-	+	-	-	-	-	+	+	-	+	-	+	-	+	-	A	+	+	-	-	+	+	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR															X										
PROSTATE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OSTEOSARCOMA, INVASIVE																									
SPECIAL SENSE ORGANS																									
LACRIMAL 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																			
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
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE					X																				
MALIGNANT LYMPHOMA, MIXED TYPE																									
EOSINOPHILIC LEUKEMIA																			X						X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	090	105	071	060	105	105	075	105	105	105	091	105	105	099	105	105	105	105	091	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROSARCOMA								X																		1
OSTEOSARCOMA						X																				1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA		X													X						X					4
ALVEOLAR/BRONCHIOLAR ADENOMA											X													X		3
ALVEOLAR/BRONCHIOLAR CARCINOMA																X										1
OSTEOSARCOMA, METASTATIC						X																				1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA																	X									1
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA																								X		2
LYMPH NODES	+	+	-	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	-	41
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																						X				1
THYMUS	+	+	+	+	+	-	-	+	+	-	+	-	-	A	+	+	-	-	+	+	-	+	+	-	+	34
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA	X											X														4
HEPATOCELLULAR CARCINOMA		X		X	X					X				X				X		X	X	X				12
HEMANGIOSARCOMA																	X									2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	N	+	+	N	N	N	+	+	+	+	+	+	+	N	N	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	-	+	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	38
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA																								X		2
PHEOCHROMOCYTOMA		X																								2
THYROID	+	+	+	+	+	+	+	+	-	+	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	46
PARATHYROID	+	+	+	-	-	+	-	-	-	-	-	-	-	A	+	-	-	-	+	-	-	+	+	-	-	19
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	48
ISLET-CELL ADENOMA													X													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	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR																										1
PROSTATE	+	+	+	+	+	+	+	+	+	-	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
OSTEOSARCOMA, INVASIVE						X																				1
SPECIAL SENSE ORGANS																										
LACRIMAL 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											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*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																	X									1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																		X		X						4
MALIGNANT LYMPHOMA, MIXED TYPE																										1
EOSINOPHILIC LEUKEMIA						X																				1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	091	105	105	105	105	105	105	105
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA								X	X																
ALVEOLAR/BRONCHIOLAR ADENOMA													X							X					
ALVEOLAR/BRONCHIOLAR CARCINOMA								X				X						X							
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	-	+	+	-	+
THYMUS	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA					X					X							X	X	X						X
HEPATOCELLULAR CARCINOMA								X	X							X								X	X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	N	+	N	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA			X																						
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA											X														
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS				X																					
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
FOLLICULAR-CELL ADENOMA																									
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
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR																			X						
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	X				X	X																			

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL
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 6	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
HEPATOCELLULAR CARCINOMA, METASTA																										2
ALVEOLAR/BRONCHIOLAR ADENOMA																					X					3
ALVEOLAR/BRONCHIOLAR CARCINOMA									X					X												5
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	•	50
LYMPH NODES	+	+	+	+	-	+	+	+	+	+	+	+	+	•	-	+	+	+	+	+	+	+	+	+	+	47
THYMUS	+	+	+	+	+	+	+	-	+	+	-	+	-	-	+	+	+	+	-	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA														X				X								9
HEPATOCELLULAR CARCINOMA			X														X				X				4
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	N	N	N	+	N	+	+	N	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOMA																										1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	-	+	-	+	+	+	+	41
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																		X								1
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	N	N	N	N	N	N	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR																										1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	N	50M
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
1: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	094	095	107	105	105	086	092	105	105	076	105	105	105	105	105	105	105	105	105	105	096	105	103	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA																									
LEIOMYOSARCOMA																									
OSTEOSARCOMA											X														
OSTEOSARCOMA, INVASIVE										X															
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA											X														
OSTEOSARCOMA, METASTATIC										X															
TRACHEA	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																							X		
THYMUS	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	-	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	-	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																									X
HEPATOCELLULAR CARCINOMA																							X		
HEPATOBLASTOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	N	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																						X			
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																	X								
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	-	+	+	+	+	+	+	-	-	+	-	+	+	-	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
PARATHYROID	-	+	-	+	+	-	-	-	+	-	+	+	-	+	+	-	+	-	-	+	+	+	-	+	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									X
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	N	N	N	+	N	N	+	+	N	+	N	+	+	+	N	+	+	+	+	+	+
ACINAR-CELL CARCINOMA																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP							X												X	X					
HEMANGIOMA															X										
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL TUMOR																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OSTEOSARCOMA, METASTATIC										X															
SPINAL CORD	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, INVASIVE										X															
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
OSTEOSARCOMA										X															
BODY CAVITIES																									
MESENTERY	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																									
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
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			X	X		X															X				
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	X								X																
MALIGNANT LYMPHOMA, MIXED TYPE					X																				
LYMPHOCYTIC LEUKEMIA																		X	X						

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	077	105	076	105	071	088	105	096	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
BASAL-CELL CARCINOMA																	X									1
LEIOMYOSARCOMA													X													1
OSTEOSARCOMA																										1
OSTEOSARCOMA, INVASIVE																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
OSTEOSARCOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA					X																					1
LYMPH NODES	+	-	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	43
MALIG.LYMPHOMA, HISTIOCYTIC TYPE														X												2
THYMUS	+	-	+	+	+	+	+	-	+	+	+	+	+	+	-	-	-	-	+	+	+	+	-	+		36
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA			X																					X		2
HEPATOCELLULAR CARCINOMA																										1
HEPATOBLASTOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	+	N	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+		50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	43
CARCINOMA,NOS												X														1
ADENOMA, NOS			X																		X					2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA		X																					X			2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	44
FOLLICULAR-CELL CARCINOMA												X														1
PARATHYROID	-	+	-	-	-	+	-	+	+	+	+	+	+	-	-	+	-	-	+	+	-	-	+	+	+	27
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	N	+	+	N	+	+	+	+	+	50*
ACINAR-CELL CARCINOMA																						X				1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP																										3
HEMANGIOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULOSA-CELL TUMOR																								X		1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
OSTEOSARCOMA, METASTATIC																										1
SPINAL CORD	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, INVASIVE																										1
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*
OSTEOSARCOMA																										1
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N	N	50*
HEMANGIOSARCOMA																										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*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																						X				5
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										2
MALIGNANT LYMPHOMA, MIXED TYPE																										1
LYMPHOCYTIC LEUKEMIA																								X		1

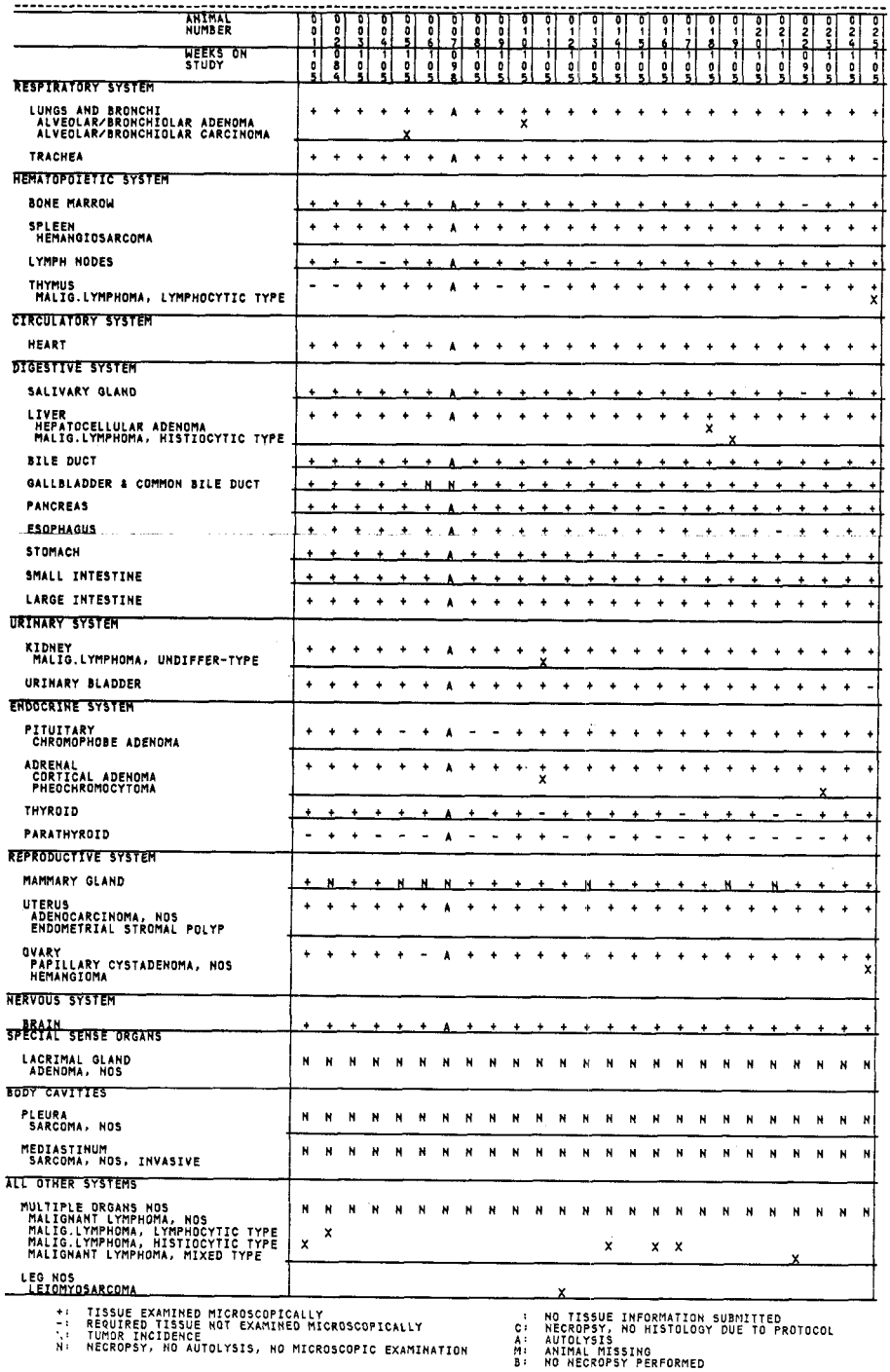
* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: *TUMOR INCIDENCE*
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

LOW DOSE



+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	074	083	091	105	105	105	105	105	105	105	065	062	105	105	105	079	105	081	105	105	081	105	105	105	105	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA				X																						2
ALVEOLAR/BRONCHIOLAR CARCINOMA						X																				2
TRACHEA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA					X																					1
LYMPH NODES	-	-	-	+	+	+	-	+	+	+	+	+	+	-	+	A	-	+	+	+	+	-	+	+		38
THYMUS	-	+	+	-	+	+	+	+	+	+	+	-	+	+	+	A	-	+	+	+	-	-	+	+		37
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	50M
PANCREAS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	46
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	A	+	+	+	+	+	+	+	+	+	46
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	A	+	-	+	+	+	+	+	+	+	46
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, UNDIFFER-TYPE																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	A	+	+	-	+	+	-	+	+		42
CHROMOPHOBE ADENOMA	X																				X					2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	49
PARATHYROID	-	-	-	+	-	-	-	-	-	+	-	-	+	+	+	A	-	-	+	-	+	+	+	+		21
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	N	+	+	+	N	+	N	+	+	N	+	N	+	+	+	+	+	+	+	50M
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
ADENOCARCINOMA, NOS		X																								1
ENDOMETRIAL STROMAL POLYP								X		X																2
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	-	+	+	45
PAPILLARY CYSTADENOMA, NOS																										1
HEMANGIOMA																			X							1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
LACRIMAL 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	50M
ADENOMA, NOS															X											1
BODY CAVITIES																										
PLEURA	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	50M
SARCOMA, NOS							X																			1
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	50M
SARCOMA, NOS, INVASIVE							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	50M
MALIGNANT LYMPHOMA, NOS									X																	1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				X																		X				3
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			X																							5
MALIGNANT LYMPHOMA, MIXED TYPE																										1
LEG NOS																										
LEIOMYOSARCOMA																										1

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF L-ASCORBIC ACID

HIGH DOSE

ANIMAL NUMBER	0012	0023	0034	0045	0056	0067	0078	0089	0100	0111	0122	0133	0144	0155	0166	0177	0188	0199	0201	0212	0223	0234	0245
WEEKS ON STUDY	105	108	109	105	105	105	105	105	105	109	110	105	108	105	105	105	103	106	105	109	104	105	105
INTEGUMENTARY SYSTEM																							
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
SARCOMA, NOS																			X				
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																							
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA							X																
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA							X																
LYMPH NODES	+	+	+	+	–	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+
FIBROSARCOMA																						X	
FIBROSARCOMA, INVASIVE																							
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																					X		
MALIGNANT LYMPHOMA, MIXED TYPE																							
THYMUS	+	–	+	–	+	+	+	–	+	+	+	+	+	–	+	+	–	–	–	+	–	+	+
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA													X										
HEPATOCELLULAR CARCINOMA														X									
HEMANGIOSARCOMA															X								
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	N	+	+	+	+	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
ESOPHAGUS	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
FIBROSARCOMA																							
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
ENDOCRINE SYSTEM																							
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+
ADENOMA, NOS																							
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																						X	X
THYROID	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+
PARATHYROID	–	–	+	–	–	+	+	+	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
ISLET-CELL ADENOMA											X												
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND	+	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	N	+	+	N	N	+	+	+
ACINAR-CELL CARCINOMA																							
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																							X
HEMANGIOSARCOMA																							X
OVARY	+	+	+	+	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
TERATOMA, NOS																					X		
NERVOUS SYSTEM																							
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																							
LACRIMAL GLAND	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												X											
MUSCULOSKELETAL SYSTEM																							
MUSCLE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N
HEMANGIOSARCOMA																							
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
MALIGNANT LYMPHOMA, NOS																			X				
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		X											X	X									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																							
MALIGNANT LYMPHOMA, MIXED TYPE			X																				
GRANULOCYTIC LEUKEMIA																							
BASE OF TAIL																							
SARCOMA, NOS																							

+: TISSUE EXAMINED MICROSCOPICALLY
–: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	090	105	105	083	105	105	105	105	105	105	091	105	105	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS													X													2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA								X																		1
TRACHEA	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																										1
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																										1
LYMPH NODES	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	43
FIBROSARCOMA																										1
FIBROSARCOMA, INVASIVE						X																				1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																					X		X			3
MALIGNANT LYMPHOMA, MIXED TYPE				X																						1
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	39
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA						X																				2
HEPATOCELLULAR CARCINOMA																										1
HEMANGIOSARCOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FIBROSARCOMA						X																				1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOMA, NOS														X												1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																										2
THYROID	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	-	+	+	+	43
PARATHYROID	-	+	-	+	+	-	+	+	+	-	-	+	+	-	+	+	-	+	+	+	+	-	-	-	-	30
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	50M
ACINAR-CELL CARCINOMA				X																						1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROSARCOMA																	X									1
HEMANGIOSARCOMA																										2
OVARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
TERATOMA, NOS																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
LACRIMAL 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	50M
ADENOCARCINOMA, NOS																										1
MUSCULOSKELETAL SYSTEM																										
MUSCLE	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	50M
HEMANGIOSARCOMA																								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	50M
MALIGNANT LYMPHOMA, NOS						X			X							X								X	X	5
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE														X								X				3
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										3
MALIGNANT LYMPHOMA, MIXED TYPE		X																								1
GRANULOCYTIC LEUKEMIA																										1
BASE OF TAIL																										
SARCOMA, NOS																							X			1

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
.: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX C

SUMMARY OF INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED DIETS CONTAINING L-ASCORBIC ACID

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DIETS CONTAINING L-ASCORBIC ACID

	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			1 (2%)
ACANTHOSIS			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
CYST, NOS		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
*NASAL TURBINATE	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
#LUNG	(49)	(50)	(50)
EDEMA, NOS			1 (2%)
HEMORRHAGE	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, INTERSTITIAL	2 (4%)		
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		2 (4%)
PNEUMONIA INTERSTITIAL CHRONIC	1 (2%)		
GRANULOMA, NOS	1 (2%)		
GRANULOMA, FOREIGN BODY			1 (2%)
NECROSIS, FOCAL	1 (2%)		
HEMOSIDEROSIS		2 (4%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	3 (6%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(50)	(49)
HYPERPLASIA, RETICULUM CELL			1 (2%)
#SPLEEN	(48)	(50)	(49)
CONGESTION, ACUTE		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FIBROSIS, FOCAL			2 (4%)
FIBROSIS, DIFFUSE			1 (2%)
NECROSIS, FOCAL	1 (2%)	1 (2%)	
#SPLENIC RED PULP	(48)	(50)	(49)
FIBROSIS, FOCAL	1 (2%)		
LYMPHOID DEPLETION			1 (2%)
#LYMPH NODE	(45)	(42)	(48)
EDEMA, NOS		1 (2%)	
HEMORRHAGE		1 (2%)	
#MANDIBULAR L. NODE	(45)	(42)	(48)
HEMORRHAGE	4 (9%)		1 (2%)
ANGIECTASIS	2 (4%)		1 (2%)
PLASMACYTOSIS	2 (4%)		
#MESENTERIC L. NODE	(45)	(42)	(48)
ANGIECTASIS	5 (11%)	6 (14%)	4 (8%)
#THYMIC MEDULLA	(40)	(43)	(42)
HYPERPLASIA, EPITHELIAL	1 (3%)		
CIRCULATORY SYSTEM			
#MEDULLA OBLONGATA	(49)	(50)	(49)
PERIVASCULITIS	1 (2%)		
#LUNG	(49)	(50)	(50)
PERIVASCULITIS	1 (2%)		1 (2%)
#HEART	(49)	(50)	(50)
DILATATION, NOS		1 (2%)	
DEGENERATION, NOS		1 (2%)	
DEGENERATION, MUCOID	1 (2%)		
#HEART/ATRIUM	(49)	(50)	(50)
THROMBUS, MURAL	2 (4%)	2 (4%)	1 (2%)
#LEFT ATRIUM	(49)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#MYOCARDIUM	(49)	(50)	(50)
EDEMA, INTERSTITIAL		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DEGENERATION, NOS	42 (86%)	43 (86%)	42 (84%)
*CORONARY ARTERY	(50)	(50)	(50)
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
PERIVASCULITIS			1 (2%)
*RENAL ARTERY	(50)	(50)	(50)
PERIVASCULITIS		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(50)	(50)
ATROPHY, FOCAL		1 (2%)	
METAPLASIA, SQUAMOUS			1 (2%)
#LIVER	(49)	(50)	(50)
CYST, NOS			1 (2%)
CONGESTION, CHRONIC PASSIVE		1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
GRANULOMA, NOS	1 (2%)	2 (4%)	2 (4%)
DEGENERATION, NOS			1 (2%)
NECROSIS, FOCAL	2 (4%)	1 (2%)	2 (4%)
NECROSIS, COAGULATIVE	1 (2%)		
BASOPHILIC CYTO CHANGE	32 (65%)	27 (54%)	27 (54%)
FOCAL CELLULAR CHANGE	2 (4%)		
ANGIECTASIS		1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(49)	(50)	(50)
NECROSIS, FOCAL		1 (2%)	3 (6%)
#LIVER/HEPATOCYTES	(49)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
#BILE DUCT	(49)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
HYPERPLASIA, FOCAL	11 (22%)	21 (42%)	10 (20%)
HYPERPLASIA, DIFFUSE	1 (2%)		
#PANCREATIC ACINUS	(49)	(50)	(49)
NECROSIS, FOCAL		1 (2%)	
ATROPHY, FOCAL	19 (39%)	9 (18%)	16 (33%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#ESOPHAGEAL SUBMUCOSA	(48)	(49)	(49)
GRANULOMA, FOREIGN BODY			1 (2%)
#ESOPHAGEAL ADVENTITI	(48)	(49)	(49)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#STOMACH	(49)	(50)	(50)
ULCER, ACUTE		1 (2%)	
#GASTRIC MUCOSA	(49)	(50)	(50)
NECROSIS, FOCAL		1 (2%)	
#CARDIAC STOMACH	(49)	(50)	(50)
VESICLE	1 (2%)		
ULCER, ACUTE	1 (2%)		
INFLAMMATION, ACUTE FOCAL	2 (4%)		1 (2%)
ULCER, CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL			2 (4%)
#GASTRIC FUNDUS	(49)	(50)	(50)
MINERALIZATION	1 (2%)		
NECROSIS, FOCAL			1 (2%)
#PYLORUS	(49)	(50)	(50)
NECROSIS, FOCAL	1 (2%)		
#COLON	(45)	(50)	(48)
NEMATODIASIS	2 (4%)	3 (6%)	10 (21%)
#CECUM	(45)	(50)	(48)
EDEMA, NOS		2 (4%)	
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
MINERALIZATION	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
NEPHROPATHY	43 (88%)	45 (90%)	46 (92%)
PIGMENTATION, NOS	1 (2%)	5 (10%)	
BASOPHILIC CYTO CHANGE		1 (2%)	
#KIDNEY/TUBULE	(49)	(50)	(50)
DILATATION, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PIGMENTATION, NOS	2 (4%)	1 (2%)	1 (2%)
#URINARY BLADDER	(48)	(49)	(49)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
#U. BLADDER/MUCOSA	(48)	(49)	(49)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
*PROSTATIC URETHRA	(50)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(45)	(50)
CYST, NOS		1 (2%)	
MULTIPLE CYSTS		1 (2%)	
HEMORRHAGE	2 (4%)		
GLIOSIS	1 (2%)	2 (4%)	
DEGENERATION, CYSTIC			1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
HYPERPLASIA, CHROMOPHOBE-CELL		1 (2%)	2 (4%)
ANGIECTASIS	1 (2%)	1 (2%)	
#ADRENAL	(49)	(50)	(50)
HYPERTROPHY, FOCAL			1 (2%)
#ADRENAL CORTEX	(49)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
NECROSIS, COAGULATIVE	1 (2%)		
LIPOIDOSIS	5 (10%)	4 (8%)	
CYTOPLASMIC VACUOLIZATION		1 (2%)	
FOCAL CELLULAR CHANGE	1 (2%)		
HYPERTROPHY, FOCAL	1 (2%)		1 (2%)
HYPERPLASIA, FOCAL	5 (10%)	7 (14%)	7 (14%)
#ZONA FASCICULATA	(49)	(50)	(50)
LIPOIDOSIS		1 (2%)	
#ADRENAL MEDULLA	(49)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	2 (4%)	4 (8%)	6 (12%)
ANGIECTASIS	1 (2%)		
#THYROID	(49)	(50)	(50)
FOLLICULAR CYST, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, C-CELL	16 (33%)	12 (24%)	19 (38%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	
#PARATHYROID	(37)	(42)	(40)
HYPERPLASIA, NOS	1 (3%)		
#PANCREATIC ISLETS	(49)	(50)	(49)
HYPERPLASIA, FOCAL	2 (4%)	9 (18%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
MULTIPLE CYSTS	2 (4%)	3 (6%)	1 (2%)
CYSTIC DUCTS	1 (2%)		
HYPERPLASIA, CYSTIC		1 (2%)	1 (2%)
*PREPUCE	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
HYPERKERATOSIS			1 (2%)
#PROSTATE	(49)	(50)	(47)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
INFLAMMATION ACUTE AND CHRONIC	2 (4%)		
INFLAMMATION, CHRONIC FOCAL	2 (4%)		
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL	1 (2%)		
#PROSTATIC GLAND	(49)	(50)	(47)
HYPERPLASIA, FOCAL	1 (2%)		
#TESTIS	(50)	(50)	(49)
ATROPHY, NOS	1 (2%)		
HYPERPLASIA, INTERSTITIAL CELL	4 (8%)	3 (6%)	4 (8%)
#TESTIS/TUBULE	(50)	(50)	(49)
DEGENERATION, NOS	1 (2%)	2 (4%)	1 (2%)
*EPIDIDYMIS	(50)	(50)	(50)
GRANULOMA, SPERMATIC	1 (2%)		1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(49)	(50)	(49)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#CEREBRUM	(49)	(50)	(49)
HEMORRHAGE	1 (2%)		
#BRAIN	(49)	(50)	(49)
NECROSIS, HEMORRHAGIC	1 (2%)	1 (2%)	
#HYPOTHALAMUS	(49)	(50)	(49)
ATROPHY, PRESSURE	1 (2%)	1 (2%)	
#CEREBELLUM	(49)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
NECROSIS, HEMORRHAGIC	1 (2%)		
#MEDULLA OBLONGATA	(49)	(50)	(49)
MALACIA			1 (2%)
NECROSIS, HEMORRHAGIC	2 (4%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
SYNECHIA, POSTERIOR	1 (2%)		
*EYE/IRIS	(50)	(50)	(50)
ANGIECTASIS			1 (2%)
*EYE/RETINA	(50)	(50)	(50)
ATROPHY, NOS			1 (2%)
ATROPHY, DIFFUSE	1 (2%)		
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)
DEGENERATION, NOS			1 (2%)
*LENS CAPSULE	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*MANDIBLE	(50)	(50)	(50)
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
BODY CAVITIES			
*INGUINAL REGION	(50)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU		2 (4%)	1 (2%)
NECROSIS, FAT	2 (4%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED DIETS CONTAINING L-ASCORBIC ACID

	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			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(49)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
#LUNG	(50)	(49)	(50)
HEMORRHAGE			1 (2%)
PNEUMONIA INTERSTITIAL CHRONIC		1 (2%)	
GRANULOMA, NOS			1 (2%)
HEMOSIDEROSIS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)		2 (4%)
#LUNG/ALVEOLI	(50)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(50)	(49)
HYPERPLASIA, FOCAL		1 (2%)	
HYPERPLASIA, RETICULUM CELL			1 (2%)
#SPLEEN	(50)	(50)	(49)
INFARCT, FOCAL		1 (2%)	
HEMOSIDEROSIS	1 (2%)		
#SPLENIC FOLLICLES	(50)	(50)	(49)
NECROSIS, DIFFUSE	1 (2%)		
#LYMPH NODE	(42)	(40)	(44)
HEMORRHAGE	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MANDIBULAR L. NODE	(42)	(40)	(44)
HEMORRHAGE	3 (7%)		
GRANULOMA, NOS	2 (5%)		
#MESENTERIC L. NODE	(42)	(40)	(44)
INFLAMMATION ACUTE AND CHRONIC		1 (3%)	
ANGIECTASIS	10 (24%)	7 (18%)	5 (11%)
#HEPATIC SINUSOID	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	2 (4%)		
#THYMUS	(47)	(43)	(40)
MULTIPLE CYSTS			1 (3%)
#THYMIC CORTEX	(47)	(43)	(40)
NECROSIS, DIFFUSE	1 (2%)		
CIRCULATORY SYSTEM			
#LUNG	(50)	(49)	(50)
PERIVASCULITIS		1 (2%)	
#HEART	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
#MYOCARDIUM	(50)	(50)	(50)
DEGENERATION, NOS	43 (86%)	29 (58%)	31 (62%)
*CORONARY ARTERY	(50)	(50)	(50)
PERIVASCULITIS	1 (2%)		2 (4%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(50)
ATROPHY, FOCAL	1 (2%)		
#LIVER	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	8 (16%)	1 (2%)	
GRANULOMA, NOS	10 (20%)		8 (16%)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)	7 (14%)	
NECROSIS, FOCAL	1 (2%)	1 (2%)	2 (4%)
BASOPHILIC CYTO CHANGE	43 (86%)	34 (68%)	38 (76%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FOCAL CELLULAR CHANGE	1 (2%)		
ANGIECTASIS		1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
DEGENERATION, NOS		1 (2%)	
NECROSIS, FOCAL	2 (4%)		
#LIVER/HEPATOCYTES	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
CYTOPLASMIC VACUOLIZATION	2 (4%)		
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, FOCAL	3 (6%)	2 (4%)	2 (4%)
HYPERPLASIA, DIFFUSE			1 (2%)
#PANCREAS	(49)	(50)	(48)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
FIBROSIS, DIFFUSE	1 (2%)		
#PANCREATIC ACINUS	(49)	(50)	(48)
ATROPHY, FOCAL	7 (14%)	6 (12%)	8 (17%)
#PERIESOPHAGEAL TISSU	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
#GASTRIC MUCOSA	(50)	(50)	(49)
NECROSIS, FOCAL	1 (2%)	2 (4%)	
#GASTRIC SUBMUCOSA	(50)	(50)	(49)
EDEMA, NOS		1 (2%)	
#CARDIAC STOMACH	(50)	(50)	(49)
ULCER, ACUTE		1 (2%)	
#PEYER'S PATCH	(50)	(49)	(48)
NECROSIS, DIFFUSE	1 (2%)		
#COLON	(48)	(49)	(48)
NEMATODIASIS	5 (10%)	2 (4%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
GLOMERULONEPHRITIS, SUBACUTE	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NEPHROPATHY	25 (50%)	10 (20%)	14 (29%)
GLOMERULOSCLEROSIS, NOS	1 (2%)		
PIGMENTATION, NOS		3 (6%)	
HYPERPLASIA, TUBULAR CELL		1 (2%)	
#KIDNEY/CORTEX	(50)	(50)	(49)
PIGMENTATION, NOS		1 (2%)	1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(49)
DILATATION, NOS		1 (2%)	
NECROSIS, FOCAL	1 (2%)	1 (2%)	
PIGMENTATION, NOS	3 (6%)	1 (2%)	2 (4%)
INCLUSION, CYTOPLASMIC	1 (2%)		
#KIDNEY/PELVIS	(50)	(50)	(49)
MINERALIZATION	1 (2%)		1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(50)	(50)
CYST, NOS			2 (4%)
MULTIPLE CYSTS			3 (6%)
HEMORRHAGE		1 (2%)	
DEGENERATION, NOS	1 (2%)		
HEMOSIDEROSIS			1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
PLEOMORPHISM	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL	5 (10%)	1 (2%)	1 (2%)
ANGIECTASIS	2 (4%)		5 (10%)
#PITUITARY/BASOPHIL	(50)	(50)	(50)
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(49)
HEMORRHAGE	1 (2%)		
HEMORRHAGIC CYST	1 (2%)		
DEGENERATION, NOS	1 (2%)		
DEGENERATION, LIPOID	1 (2%)	1 (2%)	1 (2%)
NECROSIS, FOCAL	2 (4%)	1 (2%)	
LIPOIDOSIS	5 (10%)	6 (12%)	5 (10%)
HYPERTROPHY, FOCAL	3 (6%)	1 (2%)	
HYPERPLASIA, FOCAL	12 (24%)	7 (14%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANGIECTASIS	1 (2%)		
#ZONA FASCICULATA	(50)	(50)	(49)
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(49)
HYPERPLASIA, NOS			3 (6%)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	5 (10%)
HYPERPLASIA, DIFFUSE	1 (2%)		
#THYROID	(49)	(50)	(49)
HYPERPLASIA, C-CELL	28 (57%)	19 (38%)	17 (35%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
MULTIPLE CYSTS	7 (14%)	8 (16%)	8 (16%)
HYPERPLASIA, NODULAR	1 (2%)	1 (2%)	
HYPERPLASIA, CYSTIC	4 (8%)	4 (8%)	4 (8%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
*MAMMARY ACINUS	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		
*VAGINA	(50)	(50)	(50)
PROLAPSE			1 (2%)
*VAGINAL MUCOSA	(50)	(50)	(50)
ULCER, ACUTE			1 (2%)
#UTERUS	(50)	(50)	(50)
DILATATION, NOS		2 (4%)	
HEMORRHAGE		1 (2%)	
HEMORRHAGE, CHRONIC	1 (2%)		
#CERVIX UTERI	(50)	(50)	(50)
FIBROSIS		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)
#ENDOMETRIAL GLAND	(50)	(50)	(50)
CYST, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MULTIPLE CYSTS	3 (6%)	10 (20%)	8 (16%)
HYPERPLASIA, EPITHELIAL			1 (2%)
#OVARY	(50)	(50)	(50)
FOLLICULAR CYST, NOS	1 (2%)		2 (4%)
PAROVARIAN CYST	1 (2%)		1 (2%)
NERVOUS SYSTEM			
#LATERAL VENTRICLE	(50)	(50)	(50)
HYDROCEPHALUS, NOS	1 (2%)		
#CEREBRUM	(50)	(50)	(50)
NECROSIS, HEMORRHAGIC	1 (2%)		
#BRAIN	(50)	(50)	(50)
HYDROCEPHALUS, NOS		1 (2%)	1 (2%)
HYDROCEPHALUS, INTERNAL	1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
NECROSIS, HEMORRHAGIC	1 (2%)	3 (6%)	1 (2%)
#HYPOTHALAMUS	(50)	(50)	(50)
ATROPHY, PRESSURE	6 (12%)		4 (8%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE, CHRONIC			1 (2%)
*EYE/RETINA	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)
MINERALIZATION			1 (2%)
MUSCULOSKELETAL SYSTEM			
*FEMUR	(50)	(50)	(50)
OSTEOPETROSIS	27 (54%)	20 (40%)	10 (20%)
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, GRANULOMATOUS NECROSIS, FAT	1 (2%)	1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF			1

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED DIETS CONTAINING L-ASCORBIC ACID

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED DIETS CONTAINING L-ASCORBIC ACID

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
GRANULOMA, FOREIGN BODY		1 (2%)	
INFLAMMATION, NECRO GRAN			1 (2%)
NECROSIS, FAT	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(49)	(49)	(49)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
#LUNG/BRONCHIOLE	(49)	(49)	(49)
HYPERPLASIA, NOS	4 (8%)		
HYPERPLASIA, EPITHELIAL		1 (2%)	
#RESPIRATORY BRONCHIO	(49)	(49)	(49)
HYPERPLASIA, EPITHELIAL		2 (4%)	
#LUNG	(49)	(49)	(49)
EDEMA, NOS		1 (2%)	1 (2%)
HEMORRHAGE, CHRONIC		2 (4%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, INTERSTITIAL	2 (4%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
INFLAMMATION ACUTE AND CHRONIC	3 (6%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	3 (6%)	
PNEUMONIA INTERSTITIAL CHRONIC	2 (4%)	13 (27%)	8 (16%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
ALVEOLAR MACROPHAGES	2 (4%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, ALVEOLAR EPITHELIUM	10 (20%)	10 (20%)	5 (10%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(49)	(50)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
HYPERPLASIA, NEUTROPHILIC	1 (2%)		
#SPLEEN	(50)	(49)	(50)
ANGIECTASIS			1 (2%)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
HYPERPLASIA, LYMPHOID	2 (4%)		
#SPLENIC FOLLICLES	(50)	(49)	(50)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
NECROSIS, DIFFUSE	1 (2%)		
#SPLENIC RED PULP	(50)	(49)	(50)
CONGESTION, NOS	1 (2%)		
#LYMPH NODE	(36)	(41)	(43)
HEMORRHAGE			1 (2%)
PLASMACYTOSIS			1 (2%)
#MANDIBULAR L. NODE	(36)	(41)	(43)
HYPERPLASIA, LYMPHOID			1 (2%)
#MESENTERIC L. NODE	(36)	(41)	(43)
HEMORRHAGE		1 (2%)	1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (3%)		
PLASMACYTOSIS	1 (3%)		
HYPERPLASIA, LYMPHOID	2 (6%)		
#LUNG/BRONCHIOLE	(49)	(49)	(49)
HYPERPLASIA, LYMPHOID	4 (8%)	1 (2%)	
#LUNG	(49)	(49)	(49)
HYPERPLASIA, LYMPHOID		2 (4%)	
#PEYER'S PATCH	(50)	(48)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
#THYMIC CORTEX	(35)	(34)	(42)
NECROSIS, NOS			2 (5%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#RIGHT VENTRICLE	(50)	(49)	(50)
THROMBUS, MURAL			1 (2%)
#LEFT VENTRICLE	(50)	(49)	(50)
THROMBUS, MURAL			1 (2%)
#MYOCARDIUM	(50)	(49)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
DEGENERATION, NOS	1 (2%)		
PIGMENTATION, NOS		1 (2%)	
#MYOCARDIUM OF LEFT V	(50)	(49)	(50)
THROMBUS, ORGANIZED			1 (2%)
*AORTA	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
*PANCREATIC ARTERY	(50)	(50)	(50)
PERIVASCULITIS	1 (2%)		
#LIVER	(50)	(49)	(50)
THROMBUS, ORGANIZED			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(48)	(49)
ATROPHY, NOS			1 (2%)
ATROPHY, FOCAL	1 (2%)		
#LIVER	(50)	(49)	(50)
BILE STASIS			1 (2%)
CYST, NOS	1 (2%)		
INFLAMMATION, ACUTE FOCAL	3 (6%)	3 (6%)	
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
DEGENERATION, NOS	1 (2%)		2 (4%)
NECROSIS, FOCAL	4 (8%)	3 (6%)	3 (6%)
NECROSIS, COAGULATIVE		2 (4%)	
NECROSIS, ISCHEMIC	1 (2%)	1 (2%)	
BASOPHILIC CYTO CHANGE	3 (6%)		
FOCAL CELLULAR CHANGE	1 (2%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER/HEPATOCYTES	(50)	(49)	(50)
NECROSIS, FOCAL	1 (2%)		
NUCLEAR ALTERATION			1 (2%)
*GALLBLADDER	(50)	(50)	(50)
INFLAMMATION, NECRO GRAN			1 (2%)
#BILE DUCT	(50)	(49)	(50)
MULTILOCULAR CYST	1 (2%)		
#PANCREAS	(49)	(48)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
NECROSIS, FOCAL	1 (2%)		
#PANCREATIC ACINUS	(49)	(48)	(50)
ATROPHY, NOS			1 (2%)
ATROPHY, DIFFUSE	1 (2%)		
#STOMACH	(50)	(49)	(48)
HYPERPLASIA, EPITHELIAL	5 (10%)	1 (2%)	
METAPLASIA, SQUAMOUS	1 (2%)		
#GASTRIC MUCOSA	(50)	(49)	(48)
HYPERPLASIA, CYSTIC		1 (2%)	
#CARDIAC STOMACH	(50)	(49)	(48)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#PEYER'S PATCH	(50)	(48)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
#COLON	(49)	(49)	(50)
NEMATODIASIS	3 (6%)	2 (4%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(50)
MINERALIZATION	7 (14%)	1 (2%)	9 (18%)
DILATATION, NOS			1 (2%)
HYDRONEPHROSIS	1 (2%)	1 (2%)	
MULTIPLE CYSTS	1 (2%)		
PYELONEPHRITIS, NOS	1 (2%)		
PYELONEPHRITIS, FOCAL			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PYELONEPHRITIS, ACUTE			1 (2%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
PYELONEPHRITIS, ACUTE/CHRONIC	1 (2%)		
NEPHROPATHY			1 (2%)
INFARCT, FOCAL	1 (2%)	1 (2%)	
INFARCT, HEALED			1 (2%)
EOSINOPHILIC CYTO CHANGE	1 (2%)		
#KIDNEY/CORTEX	(50)	(49)	(50)
MINERALIZATION	1 (2%)	1 (2%)	1 (2%)
CYST, NOS	2 (4%)		
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
#KIDNEY/TUBULE	(50)	(49)	(50)
DILATATION, NOS			1 (2%)
DEGENERATION, NOS			1 (2%)
NECROSIS, FOCAL	2 (4%)		
REGENERATION, NOS	21 (42%)	6 (12%)	28 (56%)
#KIDNEY/PELVIS	(50)	(49)	(50)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
*URETER	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
#URINARY BLADDER	(49)	(48)	(49)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
METAPLASIA, SQUAMOUS	1 (2%)		
#U.BLADDER/SUBMUCOSA	(49)	(48)	(49)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
*URETHRA	(50)	(50)	(50)
OBSTRUCTION, NOS			1 (2%)
*PROSTATIC URETHRA	(50)	(50)	(50)
NECROSIS, FOCAL		1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL	(50)	(49)	(49)
NECROSIS, FOCAL	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERTROPHY, FOCAL		2 (4%)	1 (2%)
#ADRENAL CORTEX	(50)	(49)	(49)
FOCAL CELLULAR CHANGE		1 (2%)	
HYPERTROPHY, FOCAL	7 (14%)	4 (8%)	6 (12%)
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL MEDULLA	(50)	(49)	(49)
HYPERPLASIA, FOCAL	1 (2%)		
#THYROID	(48)	(44)	(49)
FOLLICULAR CYST, NOS	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)
#THYROID FOLLICLE	(48)	(44)	(49)
HYPERPLASIA, CYSTIC	1 (2%)		
REPRODUCTIVE SYSTEM			
*PREPUCE	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)
#PROSTATE	(48)	(47)	(50)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)
FIBROSIS, DIFFUSE	1 (2%)		
#TESTIS	(50)	(49)	(50)
MINERALIZATION	1 (2%)	1 (2%)	
ABSCESS, CHRONIC	1 (2%)		
ASPERMATOGENESIS	1 (2%)		
HYPOSPERMATOGENESIS		1 (2%)	3 (6%)
#TESTIS/TUBULE	(50)	(49)	(50)
MINERALIZATION	1 (2%)		
DEGENERATION, NOS	1 (2%)		
ATROPHY, DIFFUSE		1 (2%)	
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, EPITHELIAL		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(49)	(50)
HEMORRHAGE	1 (2%)		
SPECIAL SENSE ORGANS			
*LENS CAPSULE	(50)	(50)	(50)
DEGENERATION, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
INFLAMMATION, NECRO GRAN			1 (2%)
*MEDIASTINAL PLEURA	(50)	(50)	(50)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	5	4
AUTO/NECROPSY/HISTO PERF		1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
AUTO/NECROPSY/NO HISTO		1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED DIETS CONTAINING L-ASCORBIC ACID

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
NECROSIS, FAT			1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(49)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#LUNG/BRONCHIOLE	(49)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
#LUNG	(49)	(49)	(50)
EDEMA, NOS		1 (2%)	
HEMORRHAGE	1 (2%)		
INFLAMMATION, FOCAL	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)		1 (2%)
INFLAMMATION, ACUTE DIFFUSE		1 (2%)	
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	1 (2%)
PNEUMONIA INTERSTITIAL CHRONIC	3 (6%)	1 (2%)	5 (10%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION, GRANULOMATOUS			2 (4%)
GRANULOMA, NOS			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	6 (12%)		1 (2%)
INFLAMMATION PROLIFERATIVE			1 (2%)
HEMOSIDEROSIS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	3 (6%)	5 (10%)	3 (6%)
HISTIOCYTOSIS			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*SUBCUT TISSUE	(50)	(50)	(50)
MASTOCYTOSIS			1 (2%)
#SPLEEN	(50)	(48)	(50)
HYPERPLASIA, LYMPHOID	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIESIS	1 (2%)		
#LYMPH NODE	(43)	(38)	(43)
HYPERPLASIA, LYMPHOID	2 (5%)		
#MANDIBULAR L. NODE	(43)	(38)	(43)
HEMORRHAGE	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		
#MEDIASTINAL L.NODE	(43)	(38)	(43)
INFLAMMATION, GRANULOMATOUS			1 (2%)
#MESENTERIC L. NODE	(43)	(38)	(43)
HYPERPLASIA, LYMPHOID	1 (2%)		
MASTOCYTOSIS	1 (2%)		
#LUNG	(49)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)	2 (4%)	
#PEYER'S PATCH	(49)	(46)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
#KIDNEY	(49)	(49)	(50)
HYPERPLASIA, LYMPHOID	4 (8%)		
#THYMUS	(36)	(37)	(39)
LYMPHOID DEPLETION	1 (3%)		
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIARTERITIS	1 (2%)		
#HEART	(49)	(49)	(50)
MINERALIZATION			1 (2%)
#HEART/ATRIUM	(49)	(49)	(50)
THROMBUS, ORGANIZED		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MYOCARDIUM	(49)	(49)	(50)
MINERALIZATION	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
FIBROSIS, DIFFUSE		1 (2%)	
#MYOCARDIUM OF LEFT V	(49)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#CARDIAC VALVE	(49)	(49)	(50)
HEMOSIDEROSIS		1 (2%)	
*CORONARY ARTERY	(50)	(50)	(50)
PERIVASCULITIS		1 (2%)	
NECROSIS, FOCAL		1 (2%)	
*MESENTERIC ARTERY	(50)	(50)	(50)
PERIARTERITIS		1 (2%)	
PERIVASCULITIS	1 (2%)		
*RENAL ARTERY	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)	1 (2%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
NECROSIS, FOCAL	5 (10%)		2 (4%)
NECROSIS, COAGULATIVE			1 (2%)
BASOPHILIC CYTO CHANGE	1 (2%)		
ANGIECTASIS			1 (2%)
#PORTAL TRACT	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(49)	(50)
DEGENERATION, NOS			1 (2%)
NECROSIS, NOS			1 (2%)
#LIVER/PERIPORTAL	(50)	(49)	(50)
CYTOPLASMIC VACUOLIZATION	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREAS	(49)	(46)	(49)
CYSTIC DUCTS	1 (2%)		1 (2%)
FIBROSIS, DIFFUSE	1 (2%)		
ANGIECTASIS	1 (2%)		
#PANCREATIC DUCT	(49)	(46)	(49)
MULTIPLE CYSTS	1 (2%)		
#PANCREATIC ACINUS	(49)	(46)	(49)
ATROPHY, NOS	2 (4%)		
ATROPHY, FOCAL	1 (2%)		2 (4%)
ATROPHY, DIFFUSE	1 (2%)		
#ESOPHAGUS	(49)	(47)	(49)
HYPERPLASIA, EPITHELIAL			1 (2%)
#STOMACH	(49)	(46)	(50)
HYPERPLASIA, EPITHELIAL	2 (4%)		3 (6%)
#CARDIAC STOMACH	(49)	(46)	(50)
ULCER, FOCAL	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
#COLON	(50)	(49)	(49)
NEMATODIASIS	1 (2%)	2 (4%)	3 (6%)
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
INFARCT, ACUTE	1 (2%)		
#KIDNEY/CORTEX	(49)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
METAPLASIA, OSSEOUS	1 (2%)		
#KIDNEY/TUBULE	(49)	(49)	(50)
DEGENERATION, NOS		1 (2%)	
REGENERATION, NOS	6 (12%)		1 (2%)
#URINARY BLADDER	(48)	(48)	(48)
MINERALIZATION			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANGIECTASIS			1 (2%)
#U. BLADDER/MUCOSA	(48)	(48)	(48)
NECROSIS, FOCAL		1 (2%)	
#U.BLADDER/SUBMUCOSA	(48)	(48)	(48)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
ANGIECTASIS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(42)	(47)
HYPERPLASIA, FOCAL	1 (2%)	2 (5%)	
HYPERPLASIA, CHROMOPHOBE-CELL		1 (2%)	
#ADRENAL/CAPSULE	(50)	(48)	(50)
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL CORTEX	(50)	(48)	(50)
NECROSIS, FOCAL		1 (2%)	
HYPERTROPHY, FOCAL	1 (2%)		1 (2%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL		2 (4%)	
#ZONA GLOMERULOSA	(50)	(48)	(50)
HYPERPLASIA, FOCAL	1 (2%)		
#THYROID	(44)	(44)	(43)
COLLOID CYST			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	
#PARATHYROID	(27)	(21)	(30)
HYPERPLASIA, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
MULTIPLE CYSTS	1 (2%)		
FIBROSIS, DIFFUSE		1 (2%)	
HYPERPLASIA, CYSTIC		2 (4%)	
*MAMMARY ACINUS	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#UTERUS	(50)	(48)	(50)
DILATATION, NOS	2 (4%)	1 (2%)	1 (2%)
HEMORRHAGIC CYST			1 (2%)
HEMORRHAGE, CHRONIC	1 (2%)		
ABSCESS, CHRONIC	1 (2%)		
FIBROSIS, FOCAL	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(48)	(50)
ANGIECTASIS		2 (4%)	
#ENDOMETRIAL GLAND	(50)	(48)	(50)
MULTIPLE CYSTS	4 (8%)	8 (17%)	3 (6%)
INFLAMMATION, ACUTE	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
HYPERPLASIA, CYSTIC	39 (78%)	34 (71%)	41 (82%)
#OVARY/PAROVARIAN	(50)	(45)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
#OVARY	(50)	(45)	(46)
CYST, NOS	5 (10%)	10 (22%)	3 (7%)
FOLLICULAR CYST, NOS	1 (2%)	1 (2%)	2 (4%)
MULTILOCULAR CYST			1 (2%)
MULTIPLE CYSTS		2 (4%)	
PAROVARIAN CYST			1 (2%)
HEMORRHAGIC CYST	1 (2%)		1 (2%)
ABSCESS, CHRONIC	1 (2%)		
ANGIECTASIS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(49)	(50)
HEMORRHAGE			1 (2%)
NECROSIS, FOCAL	1 (2%)		
#HYPOTHALAMUS	(50)	(49)	(50)
ATROPHY, PRESSURE	2 (4%)	2 (4%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
SYNECHIA, ANTERIOR		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PHTHISIS BULBI	1 (2%)		
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*LARYNGEAL MUSCLE	(50)	(50)	(50)
MINERALIZATION			1 (2%)
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION ACUTE AND CHRONIC	2 (4%)		
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
NECROSIS, FAT	1 (2%)		1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		1 (2%)
BACTERIAL SEPTICEMIA		1 (2%)	
NECROSIS, FAT			1 (2%)
DEPOSIT, NOS			1 (2%)
ADIPOSE TISSUE			
INFLAMMATION, ACUTE/CHRONIC			1
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF		1	
AUTO/NECROPSY/NO HISTO		1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

ANALYSIS OF L-ASCORBIC ACID
MIDWEST RESEARCH INSTITUTE

APPENDIX E

A. ELEMENTAL ANALYSIS

Element	C	H	O
Theory	40.91	4.58	54.51
Determined			
Lot No. 7290	40.87	4.66	
	41.04	4.59	
Lot No. 0371	40.85	4.66	
	40.75	4.68	
Lot No. 2286	41.17	4.43	54.42
Lot No. 3993	40.88	4.58	54.76
	40.70	4.66	54.83
Lot No. 4779	40.86	4.64	
	40.99	4.63	

B. IODOMETRIC TITRATION (U.S. Pharmacopeia, 1975)

Results not corrected for weight loss on drying

Lot No. 7290	98.79 ± 0.02 (δ)%
Lot No. 0371	101.1 ± 0.6 (δ)%
Lot No. 2286	98.06 ± 0.16 (δ)%
Lot No. 3993	97.6 ± 0.5 (δ)%
Lot No. 4779	99.3 ± 0.5 (δ)%

C. MELTING POINT (Lot No. 7290)

Determined:	Literature Value:
190°-193°C dec (visual, scale capillary) 191°-193°C (Dupont 900 DTA)	190° - 192°C (dec) (Merck, 1976)

D. OPTICAL ROTATION (Lot No. 7290)

α_d^{24}: +22.86° ± 0.51 (δ)°	α_d^{25} 20.5° - 21.5°
(C= 1 in deoxygenated water)	(C= 1) (Merck, 1976)

E. THIN-LAYER CHROMATOGRAPHY (Lot No. 7290)

Plates: Silica Gel 60-F254;

Ref. Standard: Benzoic Acid

Amount Spotted: 100 and 300 μg

Visualization: 254 and 366 nm light and 2,4-dichlorophenol-indophenol

System 1: Methanol (100%)

R_f: 0.65-major (UV+; spray decolorizes), origin-trace
(UV+; spray, red)
R_{st}: 0.90, origin

System 2: Acetonitrile:water (80:20)
R_f: 0.29 (major) origin-trace;
R_{st}: 0.36, origin

Thin-layer chromatography is not appropriate for purity measurements because the compound is too sensitive to oxidation.

F. HIGH-PRESSURE LIQUID CHROMATOGRAPHY

1. Lot No. 7290

   Instrument: Waters ALC 202
   Detection: Ultraviolet, 254 nm
   Column: μ Carbohydrate (Waters), 300 x 4 mm
   Solvent: 1% acetic acid in water:1% acetic acid in methanol (20:80)
   Results: Major peak and one small impurity

Peak	Retention Time (min)	Retention Time (relative to major component)	Area (relative to major peak)
Impurity	3.9	0.25	**0.25**
Major	15.5	1.0	**100.00**

2. Lot No. 0371

   Instrument: Waters Programmable Component System
   Detection: Ultraviolet, 254 nm
   Column: μ Carbohydrate (Waters), 300 x 4 mm I.D.
   Solvent: 1% acetic acid in methanol, isocratic
   Sample injected: A solution (10 μl) of 1.0 mg ascorbic acid per milliliter water
   Results: Single homogenous peak with a retention time of 11.0 minutes. Systems were also tried using 1% acetic acid in methanol:1% acetic acid in water (80:20 and 50:20). No impurities were detected.

3. Lot Nos. 2286, 3993, and 4779

   Instrument System: Waters 6000A pumps, Waters 660 programmer, Waters 440 detector, Waters U6K injector
   Detection: Ultraviolet, 254 nm
   Column: Whatman Partisil PxS 10/25 PAC, 250 mm x 4.6 mm I.D.
   Solvent Systems:
   Solvent A: Water with 1% (v:v) acetic acid
   Solvent B: Methanol with 1% (v:v) acetic acid
   Program: 10% Solvent A:90% Solvent B, ioscratic
   Flow Rate: 1 ml/min

   a. Lot No. 2286
      Samples Injected: Solution (15 μl) of 0.1% ascorbic acid per milliliter of solvent B, filtered
      Results: Major peak and two impurities before the major peak with areas of 0.10% and 0.43% of the major peak area. There were no impurities after the major peak out to 38 minutes.

Peak	Retention Time (min)	Retention Time (relative to major component)	Area (relative to major peak)
1	1.9	0.24	0.10
2	3.2	0.41	0.43
3	7.8	1.00	100

b. Lot No. 3993
Samples Injected: Solution (20 μl) of 0.5 mg/ml L-ascorbic acid in solvent B
Results: Single homogeneous peak with a retention time of 7.2 minutes. Additional injections using solvent ratios of 50% A:50% B and 30% A:70% B indicated no other peaks up to 30 and 38 minutes, respectively, after injection.

Peak	Retention Time (min)	Retention Time (relative to major component)	Area (relative to major peak)
1	7.2	1.00	100

Comparison of Lot Nos. 3993 and 2286 using this same system indicated identical retention times and weight response for the major peak within the limits of experimental error.

c. Lot No. 4779
Samples Injected: Solution (20 μl) of L-ascorbic acid (0.5 mg/ml) in methanol with 1% acetic acid (v/v); filtered and stored in light-resistant vials. (Solvent System used was 80%B.)
Results: One homogeneous peak. A weight to absorbance comparison with Lot No. 3993 for major peaks indicated no difference between the two lots, within the limits of error of the analysis.

Peak	Retention Time (min)	Retention Time (relative to major component)	Area (relative to major peak)
1	9.8	1.00	100

G. SPECTRAL DATA

1. Infrared:

Instrument: Beckman IR-12

a. Lot No. 7290
Cell: 2.3% potassium bromide pellet
Results: See Figure 5; Consistent with literature spectrum (Sadtler standard spectra)

b. Lot No. 0371
Cell: 2% potassium bromide pellet
Results: See Figure 6; Consistent with literature spectrum (Sadtler standard spectra)

c. Lot No. 2286
Cell: 1.5% potassium bromide pellet
Results: See Figure 7; Consistent with literature spectrum (Sadtler standard spectra)

d. Lot Nos. 3993 and 4779
Cell: 2% potassium bromide pellet
Results: See Figures 8 and 9; Consistent with literature spectra (Sadtler standard spectra)

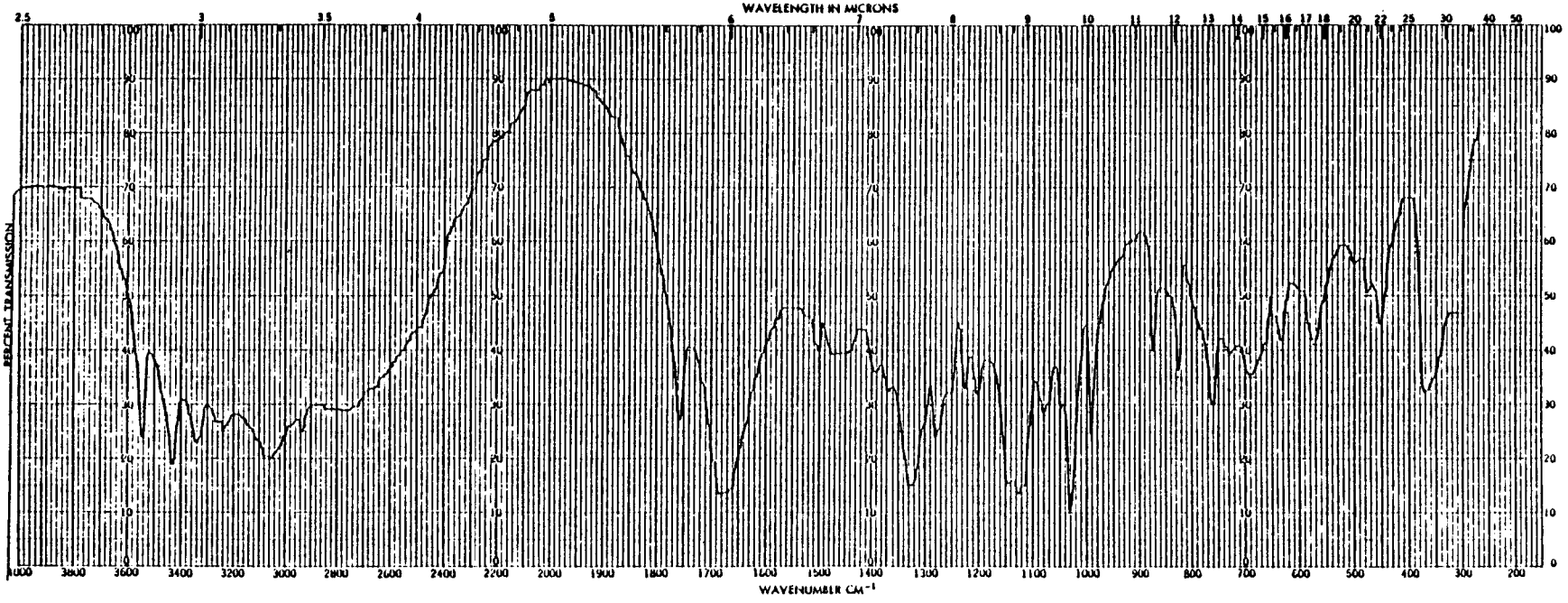


Figure 5. Infrared Absorption Spectrum of L-Ascorbic Acid (Lot No. 7290)

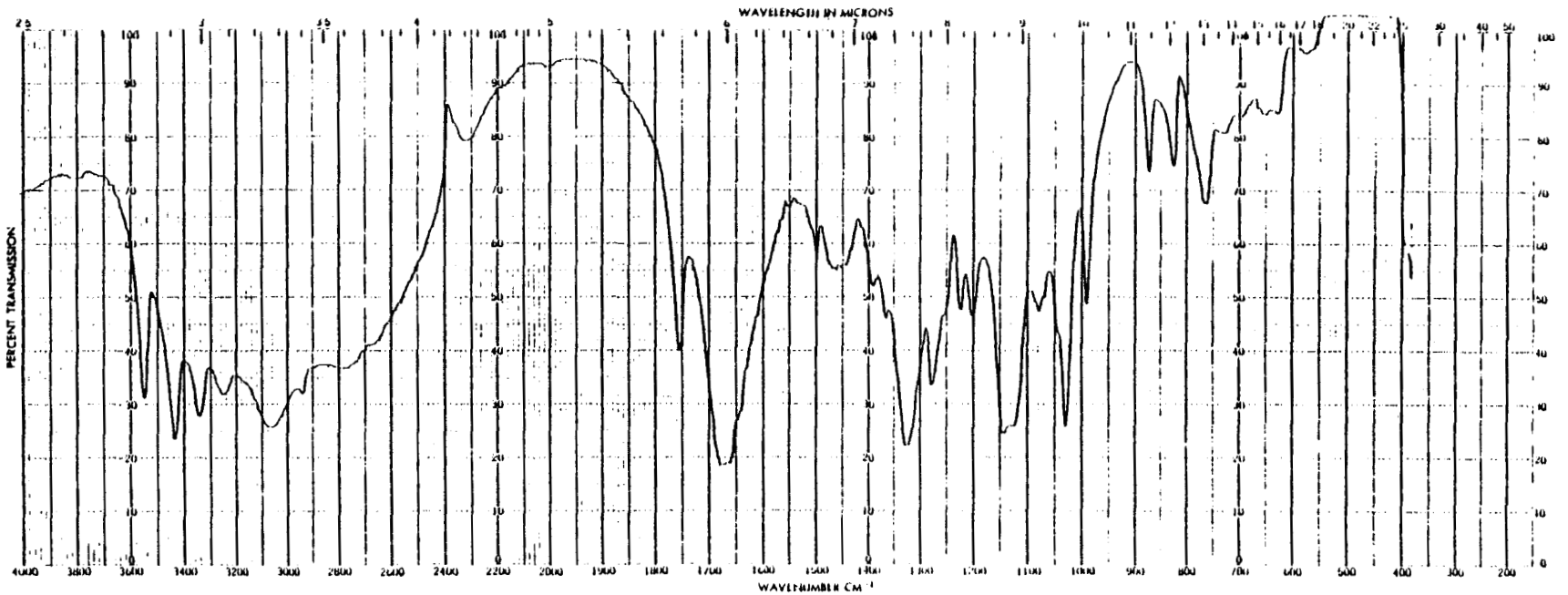


Figure 6. Infrared Absorption Spectrum of L-Ascorbic Acid (Lot No. 0371)

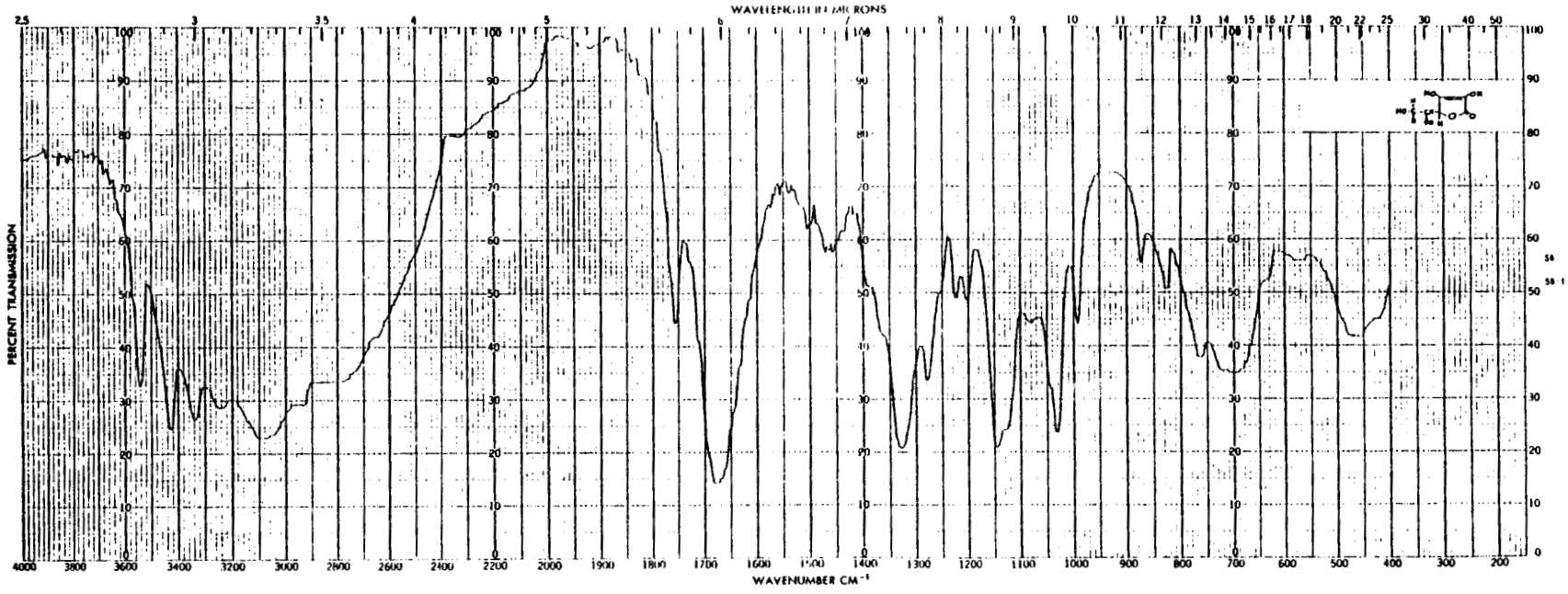


Figure 7. Infrared Absorption Spectrum of L-Ascorbic Acid (Lot No. 2286)

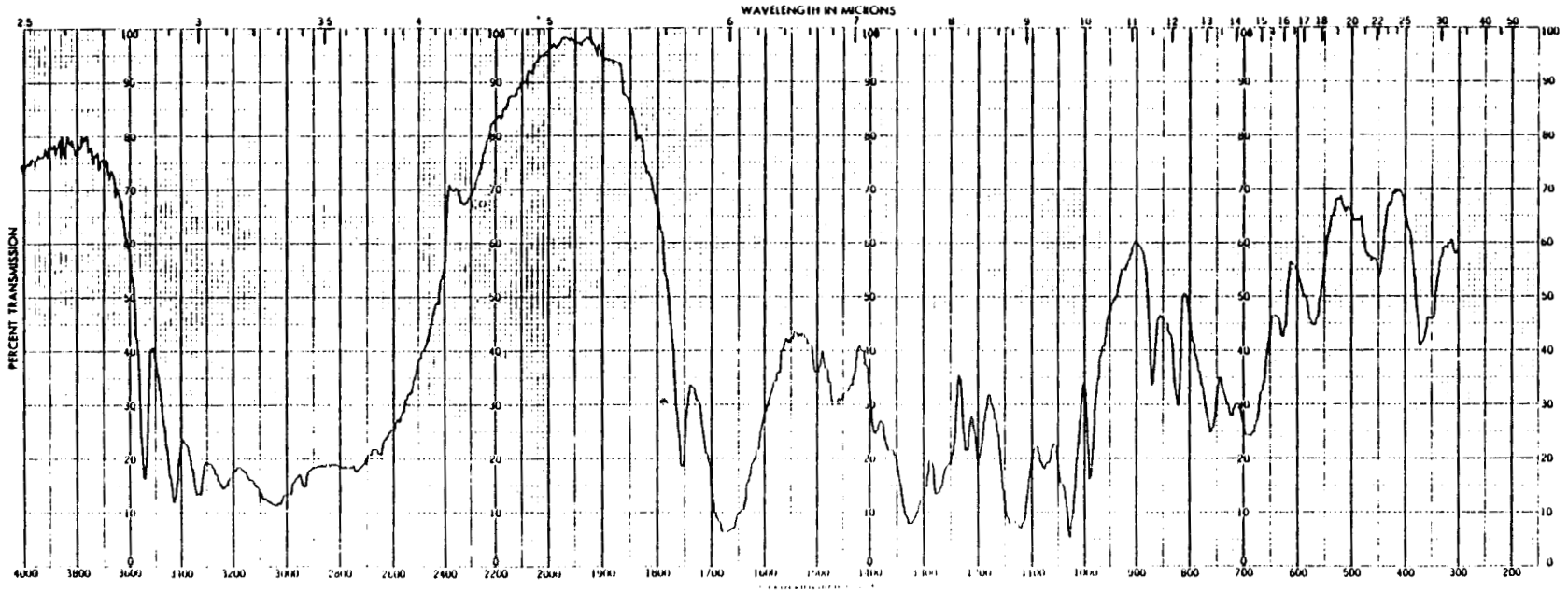


Figure 8. Infrared Absorption Spectrum of L-Ascorbic Acid (Lot No. 3993)

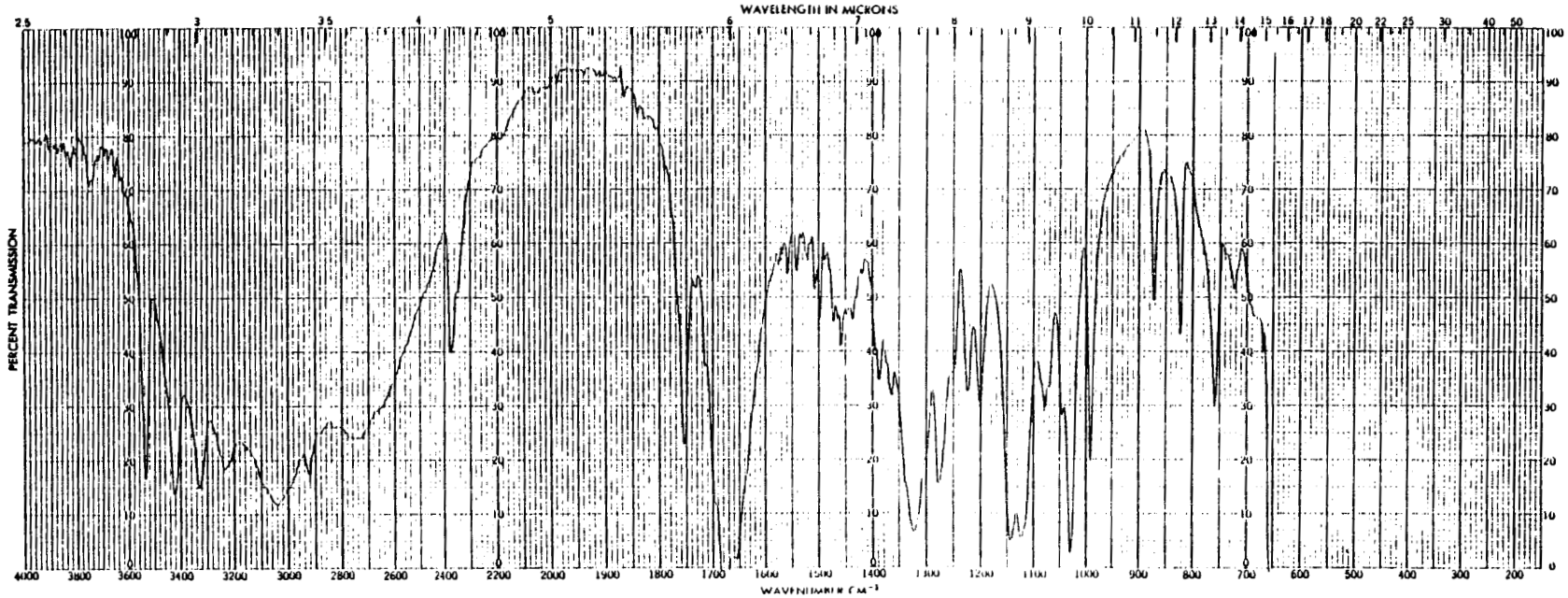


Figure 9. Infrared Absorption Spectrum of L-Ascorbic Acid (Lot No. 4779)

2. Ultraviolet/Visible:
Instrument: Cary 118

	Determined	Literature Values (Hewitt and Dickes, 1961)
a. Lot No. 7290		
$\lambda max^{(nm)}$:	265.5 nm	265 nm
$\varepsilon \times 10^{-4}$	1.516±0.005(δ)	1.65
Solvent:	Water (distilled in glass) pH 6.8, oxygen free	Sample dissolved in 2% (w/v in water) dithizone-extracted (copper-free) metaphosphoric acid which was then adjusted to pH 6.8 with trisodium phosphate and taken to volume.
b. Lot No. 0371		
$\lambda max^{(nm)}$:	265 nm	265 nm
$\varepsilon \times 10^{-4}$	1.435±0.015(δ)	1.65
Solvent:	Sample (dissolved in 2% (w/v) dithizone-extracted metaphosphoric acid in water, adjusted to pH 6.8 with trisodium phosphate and brought to volume with water	Sample dissolved in 2% (w/v) dithizone-extracted metaphosphoric acid in water adjusted to pH 6.8 with trisodium phosphate and brought to volume with water.
c. Lot No. 2286		
$\lambda max^{(nm)}$:	265nm	Same as above
$\varepsilon \times 10^{-4}$	1.520±0.010(δ)	
Solvent:	Same as Lot No. 0371	
d. Lot No. 3993		
$\lambda max^{(nm)}$:	265nm	Same as above
$\varepsilon \times 10^{-4}$	1.500±0.009(δ)	
Solvent:	Same as Lot No. 0371	
e. Lot No. 4779		
$\lambda max^{(nm)}$:	265nm	Same as above
$\varepsilon \times 10^{-4}$	1.47±0.009(δ)	
Solvent:	Deionized HPLC water, ion free	

3. Nuclear Magnetic Resonance

	Determined	Literature Values (Sadtler Standard Spectra)
a. Lot No. 7290	Instrument:Varian HA-100 Solvent:D_2O with t-butanol internal standard Assignments: See Figure 10 (a and a') d, δ 3.73, J_{ab}=6Hz (b) δ m, 4.03 (c) δ d, 4.92, J_{cd}=2Hz Integration Ratios: (a and a') 1.70 (b) 1.03 (c) 1.27	All NMR spectra were consistent with literature spectra
b. Lot No. 0371	Instrument:Varian EM-360A Solvent:D_2O with internal sodium 3-trimethylsilyl-propionate-2,2,3,3-d_4 Assignments: See Figure 11 (a and a') d of d, δ 3.70 and 3.67ppm (b) m, δ 3.93-4.27 ppm (c) d, δ 4.93 ppm Integration Ratios: (a and a') 1.95 (b) 1.05 (c) 0.97	
c. Lot No. 2286	Instrument:Varian EM-360A Solvent:Same as Lot No. 0371 Assignments: See Figure 12 (a and a') d of d, δ 3.69 and 3.72 ppm, $J_{(a \text{ or } a')\text{-}b}$ = 5Hz $J_{(a \text{ or } a')\text{-}b}$ = 7Hz (b) m, δ 3.89-4.17 ppm (c) d, δ 4.83 ppm Integration Ratios: (a and a) 2.06 (b) 0.86 (c) 1.08	

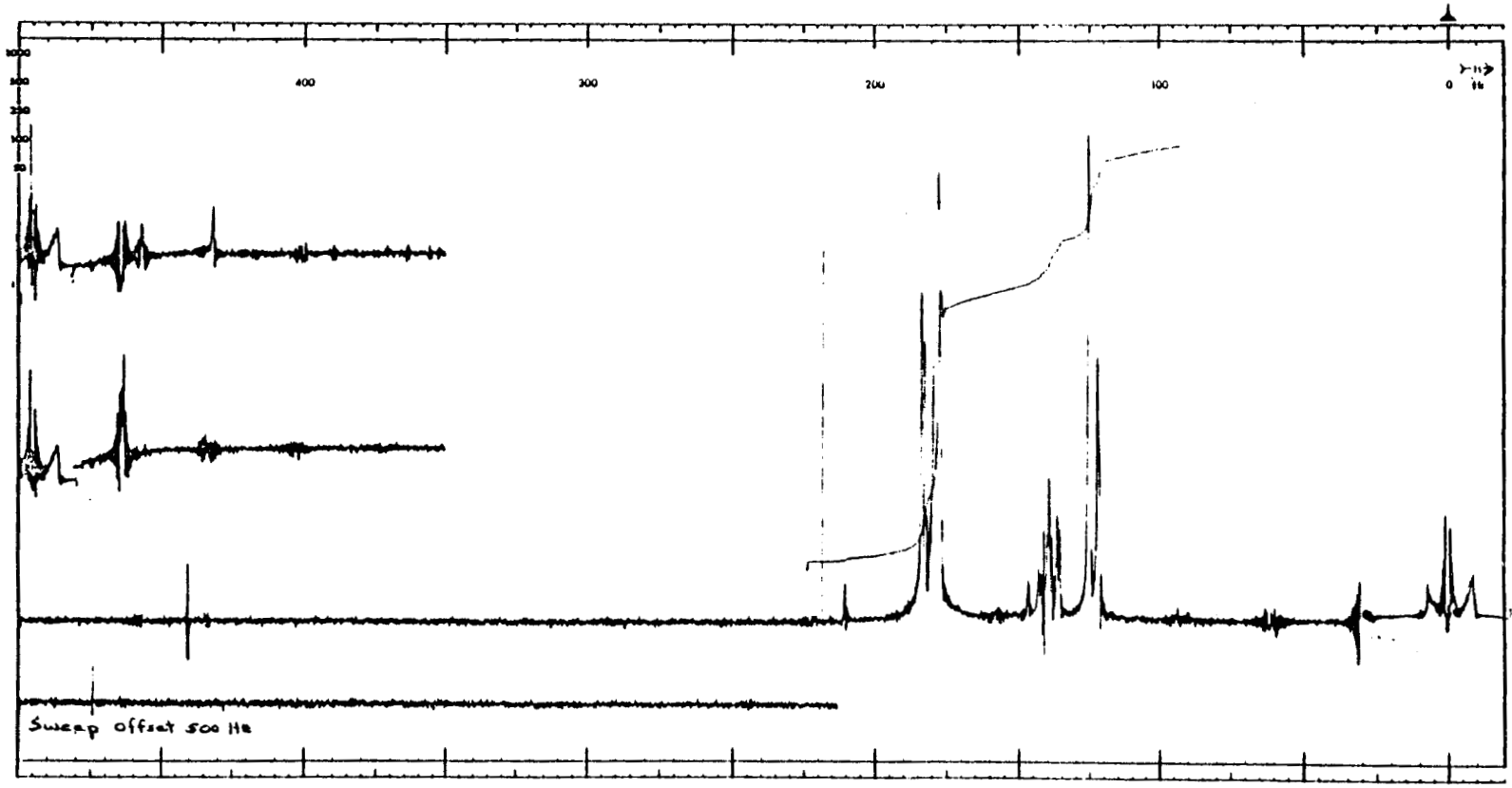


Figure 10. Nuclear Magnetic Resonance Spectrum of L-Ascorbic Acid (Lot No. 7290)

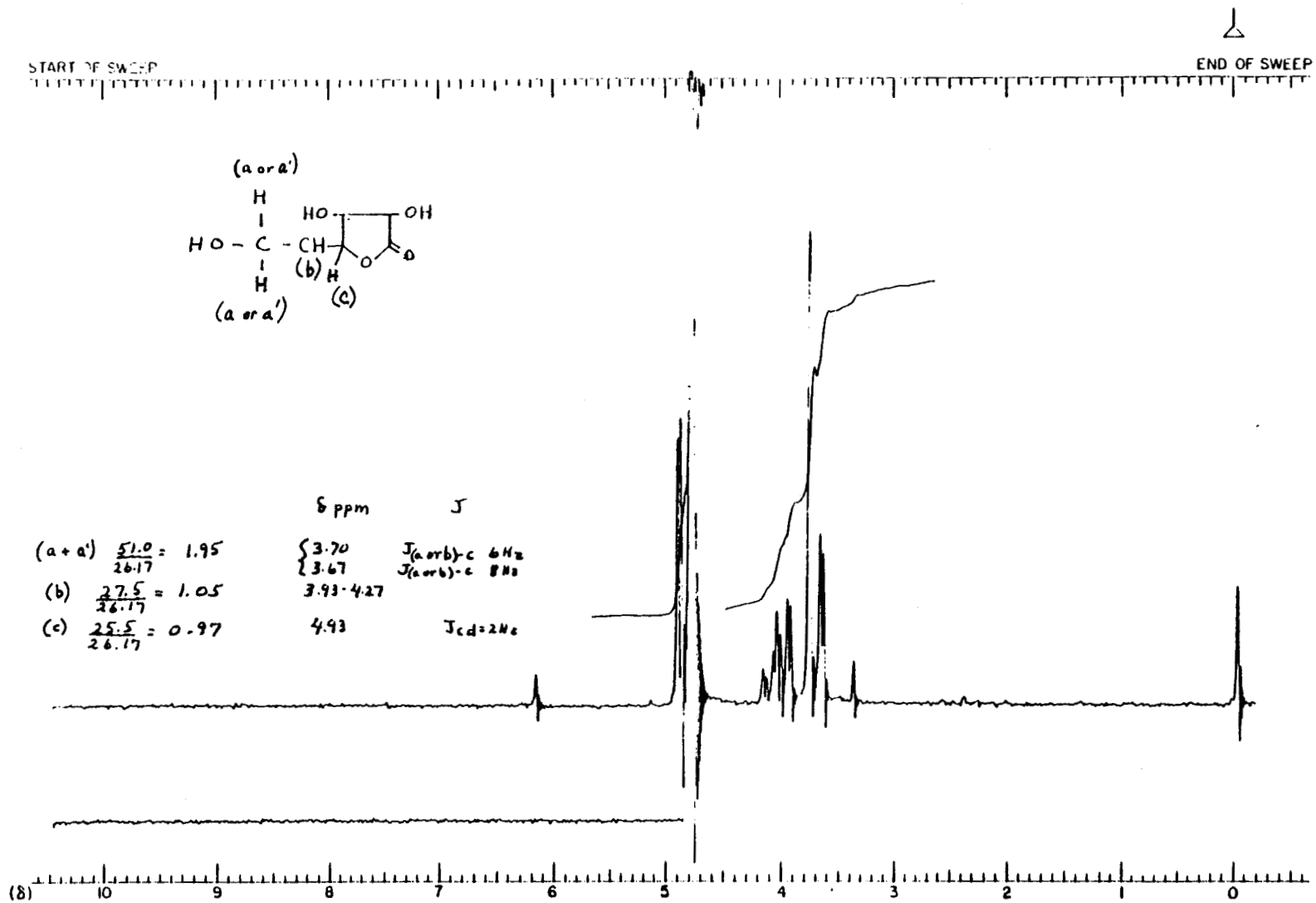


Figure 11. Nuclear Magnetic Resonance Spectrum of L-Ascorbic Acid (Lot No. 0371)

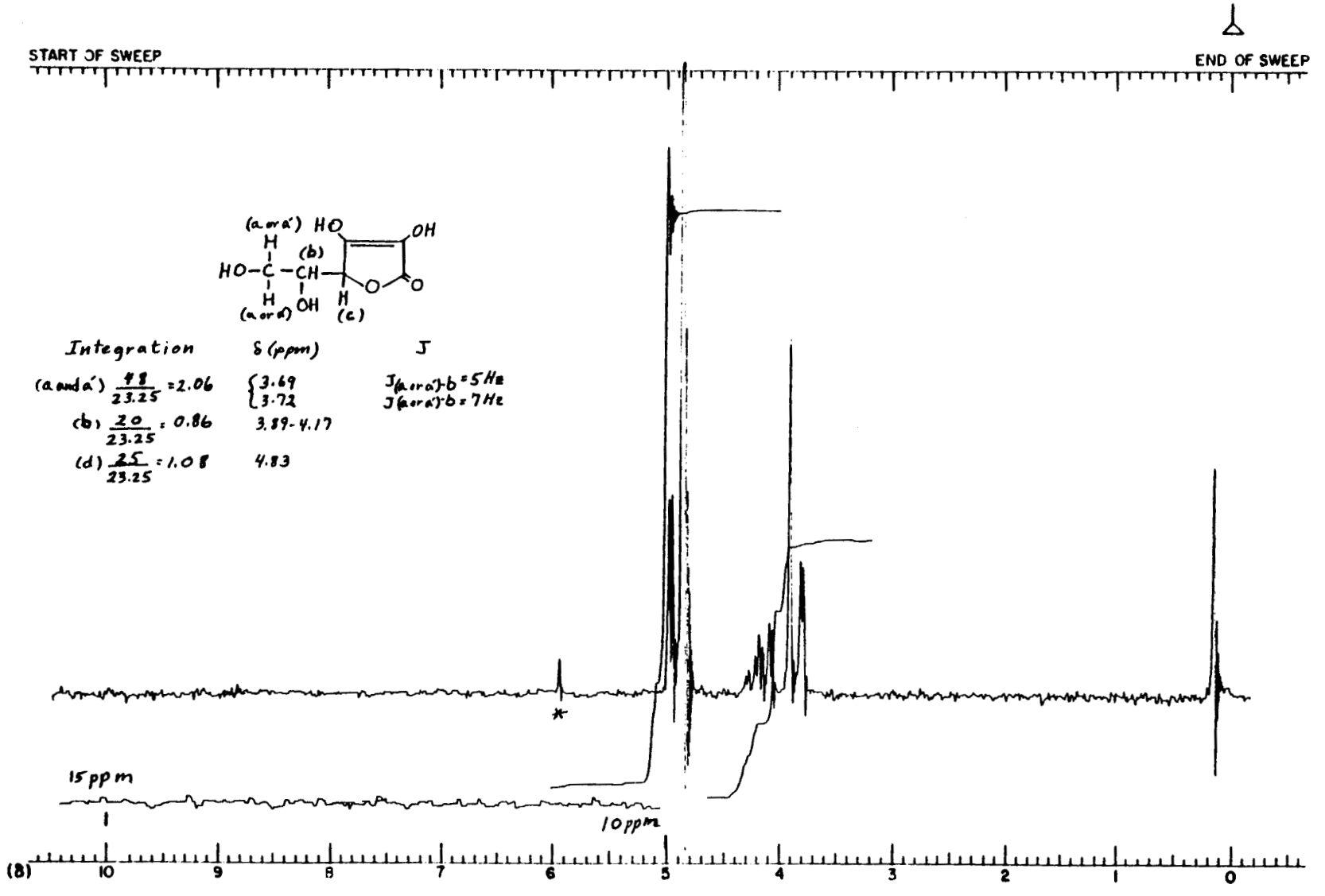


Figure 12. Nuclear Magnetic Resonance Spectrum of L-Ascorbic Acid (Lot No. 2286)

		Determined	Literature Values (Sadtler standard spectra)
d.	Lot No. 3993	Instrument:Varian EM-360A Solvent:D_2O:methanol-d_4 (1+1) with added tetramethylsilane Assignments: See Figure 13 (a and a') d of d, 3.69 ppm, d, δ 3.71 ppm $J_{(a \text{ or } a')-b}$ = 5Hz $J_{(a \text{ or } a')-b}$ = 7Hz (b) m, δ 3.88-4.20 ppm J_{b-c} = 2Hz (c) d, δ 4.91 ppm Integration Ratios: (a and a') 1.96 (b) 1.04 (c) 1.16	All NMR spectra were consistent with literature spectra
e.	Lot No. 4779	Instrument:Varian EM-360 Solvent:D_2O with sodium 3-trimethylsilyl-propionate-2,2,3,3-d_4 internal standard Assignments: See Figure 14 (a and a') d, δ 3.71 ppm, d, δ 3.75 ppm $J_{(a \text{ or } a')-b}$ = 5Hz; $J_{(a \text{ or } a')-b}$ = 7Hz; (b) m, δ 3.90-4.20 ppm J_{b-c} = 2Hz (c) d, δ , 4.91 ppm Integration Ratios: (a and a') 1.90 (b) 0.87 (c) 1.23	

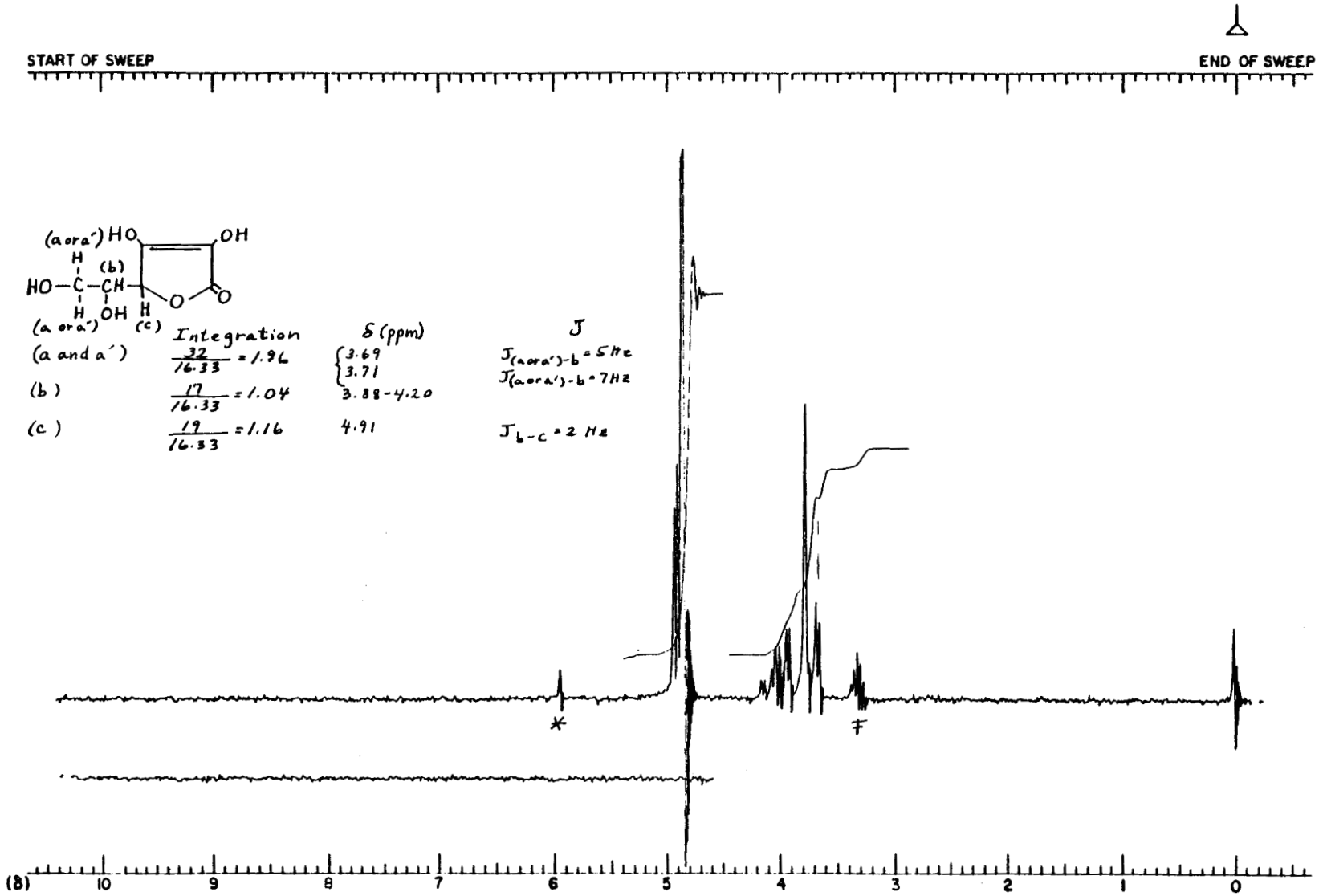


Figure 13. Nuclear Magnetic Resonance Spectrum of L-Ascorbic Acid (Lot No. 3993)

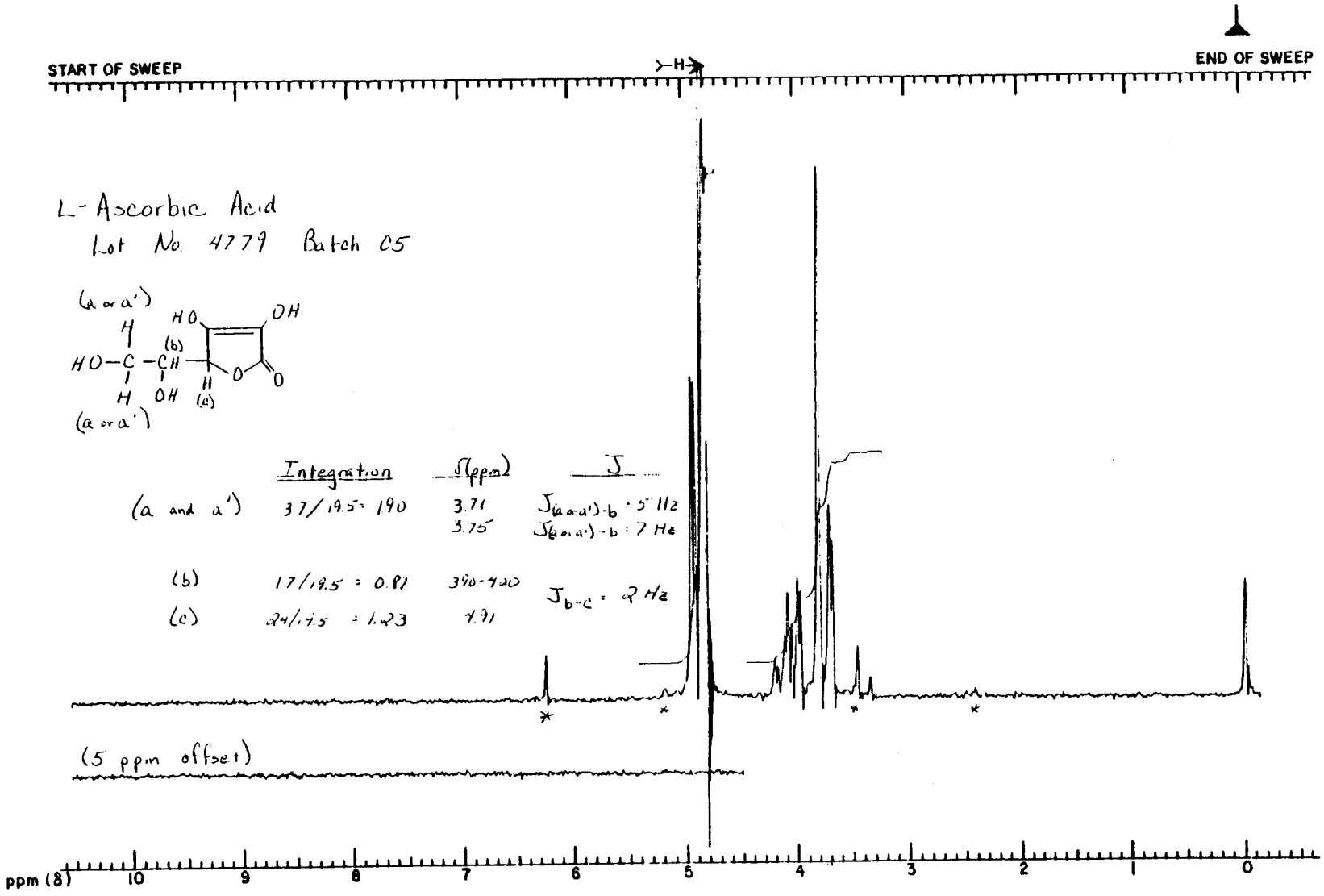


Figure 14. Nuclear Magnetic Resonance Spectrum of L-Ascorbic Acid (Lot No. 4779)

APPENDIX F

ANALYSIS OF FORMULATED DIETS FOR STABILITY OF L-ASCORBIC ACID MIDWEST RESEARCH INSTITUTE

APPENDIX F

A. MIXING AND STORAGE

L-ascorbic acid (approximately 0.1 g) and Wayne Lab-Blox® rodent feed (approximately 0.9 g) were carefully weighed out and mixed together on a vortex mixer for 1 minute. Eight samples were prepared in this manner and were stored in duplicate for 2 weeks at -20°, 5°, 25°, and 45°, respectively. The samples were then analyzed as described below.

B. EXTRACTION AND ANALYSIS PROCEDURES

One-gram amounts of the chemical feed mixture were triturated for 1 minute with 50 ml of water using a Brinkmann Polytron® blender, and this mixture was then placed in an ultrasonic vibratory bath for 30 seconds. After the samples were centrifuged for 15 minutes and the aqueous supernatant was decanted, this extraction procedure was repeated on the feed residue. The combined supernatants were then made up to volume in a 100-ml volumetric flask with additional fresh water. This solution was titrated iodimetrically in duplicate, as described below, to determine the ascorbic acid present.

C. ANALYSIS

To the diluted solution obtained in Section B, 25 ml of 1 N sulphuric acid was added. The resulting solution was immediately titrated with a standard 0.0884 N iodine solution, using a Brinkmann-Metrohm automatic titrator (conventional titration to a starch end point may also be used). Each milliliter of 0.0884 N iodine is equivalent to 7.779 mg of ascorbic acid.

Method: Iodometric titration
Instrument: Brinkmann-Metrohm Automatic Titrator

D. RESULTS

Storage Temperature (°C)	Percent Found In Chemical/Feed Mixture	Average Percent in Chemical/Feed Mixture *(a)*	Standard Deviation	Precision
-20	10.06			
-20	10.01	10.03	± 0.04	± 0.03
5	10.02			
5	9.97	9.99	± 0.04	± 0.02
25	10.08			
25	10.01	10.04	± 0.04	± 0.07
45	10.03			
45	10.07	10.05	± 0.04	± 0.04

(a) Average spiked recovery yield, 100.0% ± 0.2%. Theoretical percent in chemical/feed mixture, 10.0%. The standard deviation figure is that of all eight values and appears in the middle column. The "precision" figures are one-half the difference between the duplicate values at each storage temperature.

E. CONCLUSION

L-Ascorbic acid mixed with rodent feed at 100,000 ppm is stable when stored in tightly closed containers and protected from light for 2 weeks at temperatures of up to 45°C.

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF L-ASCORBIC ACID BATTELLE COLUMBUS LABORATORIES

APPENDIX G

Standards were prepared at the 25,000- and 50,000-ppm levels by weighing appropriate amounts of ascorbic acid into a total of 1 gram of dosed feed. Standards were shaken by hand and vortexed to assure a good mix.

Samples and standards were then extracted twice with 50-ml aliquots of deionized water. The combined supernatants were spiked with 1.0 ml of starch solution and titrated with 0.0884 N iodine solution. Each milliliter of the iodine solution is equivalent to 7.779 mg of ascorbic acid. Standards produced an average recovery of 100.8% ± 3.8%. Analyses were performed in duplicate, and concentrations reported represent values corrected for recovery (Table G1).

TABLE G1. ANALYSIS OF FORMULATED DIETS

Date Mixed *(a)*	Date Used (week of)	Concentration *(a)* of L-ascorbic acid in feed for target concentration	
		25,000 ppm	50,000 ppm
06/15/78	06/21/78	23,400	48,230
08/08/78	08/11/78	22,560	50,000
10/16/78	10/21/78	24,110	48,300
		(26,000) *(b)*	
12/11/78	12/14/78	24,110	49,800
02/06/79	02/10/79	24,800	49,900
		(25,200) *(b)*	
04/02/79	04/06/79	24,030	48,260
05/07/79	05/12/79	23,980	49,310
07/24/79	07/30/79	24,210	51,010
			(45,100) *(c)*
09/10/79	09/13/79	23,020	49,210
11/12/79	11/14/79	24,300	47,900
01/07/80	01/09/80	24,700	50,300
		(22,600) *(b)*	
03/03/80	03/05/80	24,300	
03/10/80	03/11/80		48,100
04/28/80	05/03/80	22,800	45,600
06/09/80	06/14/80	24,700	49,600
08/25/80	08/29/80	23,600	48,400
10/13/80	10/15/80	24,100	48,200
			(49,800) *(b)*
Mean (ppm)		23,916	48,699
Standard deviation		675	1,322
Coefficient of variation (%)		2.8	2.7
Range (ppm)		22,560-24,800	45,600-51,010
Number of samples		16	16

(a) The data presented are the average of the results of duplicate analyses.
(b) Results of referee analysis at MRI.
(c) Results of referee analysis at Raltech.

APPENDIX H

HISTORICAL INCIDENCES OF TUMORS IN CONTROL F344/N RATS AND B6C3F$_1$ MICE

TABLE H1. HISTORICAL INCIDENCES OF HEMATOPOIETIC TUMORS IN UNTREATED CONTROL FEMALE F344/N RATS *(a)*

Laboratory	Leukemia	Leukemia or Lymphoma
Battelle	49/288 (17.0%)	59/288 (20.5%)
Dow	3/100 (3.0%)	20/100 (20.0%)
Frederick	37/522 (7.1%)	60/522 (11.5%)
Gulf South	8/100 (8.0%)	9/100 (9.0%)
Hazleton	29/200 (14.5%)	29/200 (14.5%)
Litton	94/787 (11.9%)	106/787 (13.5%)
Mason	134/1121 (12.0%)	155/1121 (13.8%)
Papanicolaou	10/49 (20.4%)	11/49 (22.4%)
Southern	79/591 (13.4%)	91/591 (15.4%)
Total	443/3758 (11.8%)	540/3758 (14.4%)
Overall Historical Range		
High	19/50	19/50
Low	0/50	2/50

(a) Data as of June 15, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE H2. HISTORICAL INCIDENCES OF PREPUTIAL GLAND TUMORS IN UNTREATED CONTROL MALE F344/N RATS *(a)*

Laboratory	Carcinoma	Adenoma	Adenocarcinoma
Battelle	4/290 (1.4%)	4/290 (1.4%)	5/290 (1.7%)
Dow	1/100 (1.0%)	7/100 (7.0%)	0/100 (0.0%)
Frederick	2/467 (0.4%)	0/467 (0.0%)	0/467 (0.0%)
Gulf South	1/97 (1.0%)	0/97 (0.0%)	0/97 (0.0%)
Hazleton	15/198 (7.6%)	0/198 (0.0%)	0/198 (0.0%)
Litton	9/789 (1.1%)	11/789 (1.4%)	2/789 (0.3%)
Mason	19/1066 (1.8%)	28/1066 (2.6%)	0/1066 (0.0%)
Papanicolaou	0/50 (0.0%)	4/50 (8.0%)	0/50 (0.0%)
Southern	10/591 (1.7%)	7/591 (1.2%)	1/591 (0.2%)
Total	61/3648 (1.7%)	61/3648 (1.7%)	8/3648 (0.2%)
Overall Historical Range			
High	6/50	8/50	3/50
Low	0/90	0/90	0/54

(a) Data as of June 15, 1981 for studies of at least 104 weeks. Range is presented for groups of 35 or more animals.

TABLE H3. HISTORICAL INCIDENCES OF PREPUTIAL/CLITORAL GLAND TUMORS IN UNTREATED FEMALE F344/N RATS *(a)*

Laboratory	Carcinoma	Adenoma	Adenocarcinoma
Battelle	2/288 (0.7%)	1/288 (0.4%)	4/288 (1.4%)
Dow	1/100 (1.0%)	6/100 (6.0%)	0/100 (0.0%)
Frederick	1/522 (0.2%)	0/522 (0.0%)	0/522 (0.0%)
Gulf South	0/100 (0.0%)	0/100 (0.0%)	0/100 (0.0%)
Hazleton	0/200 (0.0%)	2/200 (1.0%)	0/200 (0.0%)
Litton	4/787 (0.5%)	3/787 (0.4%)	2/787 (0.3%)
Mason	23/1121 (2.1%)	11/1121 (1.0%)	0/1121 (0.0%)
Papanicolaou	0/49 (0.0%)	0/49 (0.0%)	1/49 (2.0%)
Southern	5/591 (0.8%)	7/591 (1.2%)	0/591 (0.0%)
Total	36/3758 (1.0%)	30/3758 (0.8%)	7/3758 (0.2%)
Overall Historical Range			
High	6/49	4/50	3/50
Low	0/50	0/88	0/88

(a) Data as of June 15, 1981 for studies of at least 104 weeks. Range is presented for groups of 35 or more animals.

TABLE H4. HISTORICAL INCIDENCES OF CIRCULATORY TUMORS IN UNTREATED CONTROL MALE B6C3F1 MICE *(a)*

Laboratory	Hemangiosarcoma
Battelle	4/348 (1.1%)
Dow	7/99 (7.1%)
Frederick	15/407 (3.7%)
Gulf South	1/48 (2.1%)
Hazleton	0/49 (0.0%)
Litton	5/507 (1.0%)
Mason	17/852 (2.0%)
Southern	16/640 (2.5%)
Total	65/2950 (2.2%)
Overall Historical Range	
High	5/49
Low	0/50

(a) Data as of June 15, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE H5. HISTORICAL INCIDENCES OF LIVER TUMORS IN UNTREATED CONTROL MALE B6C3F$_1$ MICE *(a)*

Laboratory	Carcinoma	Adenoma	Adenoma or Carcinoma
Battelle	30/347 (8.6%)	75/347 (21.6%)	102/347 (29.4%)
Dow	13/98 (13.3%)	33/98 (33.7%)	46/98 (46.9%)
Frederick	31/407 (7.6%)	100/407 (24.6%)	131/407 (32.2%)
Gulf South	4/48 (8.3%)	13/48 (27.1%)	16/48 (33.3%)
Hazleton	3/49 (6.1%)	17/49 (34.7%)	20/49 (40.8%)
Litton	47/499 (9.4%)	85/499 (17.0%)	132/499 (26.5%)
Mason	77/849 (9.1%)	209/849 (24.6%)	281/849 (33.1%)
Southern	65/635 (10.2%)	114/635 (18.0%)	177/635 (27.9%)
Total	270/2932 (9.2%)	646/2932 (22.0%)	905/2932 (30.9%)
Overall Historical Range			
High	11/50	24/54	29/50
Low	0/49	4/50	8/50

(a) Data as of June 15, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

APPENDIX I

HEMATOLOGIC METHODS USED IN THE 13-WEEK STUDY OF L-ASCORBIC ACID

APPENDIX I

A. Packed Cell Volume:

This volume was reported as a percentage (%) of the whole blood volume (Lynch et al., 1969; Miale, 1967) on the Coulter (Coulter Electronics, Hialeah, FL) flat pack accessory.

B. Hemoglobin:

The red cells in a specimen of blood were hemolyzed and the hemoglobin was converted into either oxy- or cyanmethemoglobin (Lynch et al., 1969; Miale, 1967). The optical density or percent transmittance of a dilute solution was measured and the hemoglobin concentration of the original sample was obtained automatically in grams percent on the Coulter Hemoglobinometer.

C. Erythrocyte Count (RBC):

Whole blood was diluted with an isotonic solution and the number of red blood cells in a known volume was counted automatically on the Coulter Counter, Model FN. RBC is expressed in $10^6/mm^3$ (Lynch et al., 1969; Miale, 1967).

D. Leukocyte Count (WBC):

Whole blood was diluted with an isotonic solution and the number of white cells in a known volume was counted automatically on a Coulter Counter, Model FN. The WBC is expressed in $10^3/mm^3$ (Lynch et al., 1969; Miale, 1967).

E. Differential:

A count of 100 leukocytes was differentiated and reported in percent per type of cell. Slides were stained with May-Grunwald/Giemsa on the Ames automatic slide stainer (Ames Co., 1974).

F. Platelet:

The platelets in a diluted sample of blood were counted in a hemocytometer. Results are reported in $10^5/mm^3$. This direct method of platelet determination was done with the Unopette disposable pipetting system (Becton-Dickinson Division, Rutherford, NJ).

G. Mean Corpuscular Volume:

Was calculated on the Coulter FN flat pack accessory.

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