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No. 236

CARCINOGENESIS BIOASSAY OF D-MANNITOL (CAS NO. 69-65-8) IN F344/N RATS AND B6C3F$_1$ 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 D-MANNITOL

(CAS NO. 69-65-8)

IN F344/N RATS AND B6C3F$_1$ MICE (FEED STUDY)

NATIONAL TOXICOLOGY PROGRAM
Box 12233
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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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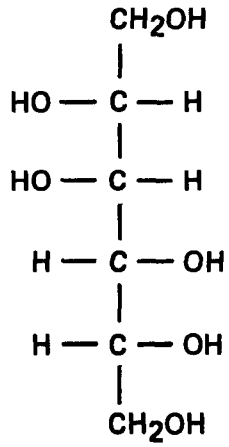

D-MANNITOL

CAS NO. 69-65-8
$C_6H_{14}O_6$ Mol. Wt. 182.17

ABSTRACT

A carcinogenesis bioassay of D-mannitol (98%-100% pure), a food and drug additive, was conducted by feeding diets containing 25,000 or 50,000 ppm D-mannitol to groups of 50 F344/N rats and 50 B6C3F1 mice of each sex for 103 weeks. Groups of 50 rats and 50 mice of each sex served as controls.

Survival and mean body weights of dosed and control male rats and of dosed and control mice of each sex were comparable. Survival of high-dose female rats was significantly higher ($P<0.05$) than that of the low-dose female rats. However, neither the survival of the low-dose group nor that of the high-dose group was significantly different from that of the controls. Throughout the study, mean body weight gain of dosed female rats was depressed ($\leq 10\%$) relative to that of controls. Feed consumption by dosed and control rats and mice of each sex was similar.

Although the rats and mice of each sex might have been able to tolerate higher doses, a dietary level of 50,000 ppm (5%) is the maximum concentration of a test substance in feed recommended in the guidelines of the Bioassay Program.

Dilatation of the gastric fundal gland was observed in increased incidence in dosed female rats when compared with that of controls (control, 6/50, 12%; low dose, 23/50, 46%; high dose 23/50, 46%). Retinopathy and cataracts occurred at increased incidences in high-dose males and in low- and high-dose female rats.

A mild nephrosis, characterized by focal vacuolization of renal tubular epithelium, was observed in increased incidence in dosed mice of each sex and was considered to be related to administration of D-mannitol (males: control, 15/50, 30%; low dose, 29/50, 58%; high dose, 30/47, 64%; females: control, 1/48, 2%; low dose, 3/48, 6%; high dose, 14/49, 29%).

Under the conditions of this bioassay, D-mannitol was not carcinogenic for F344/N rats or B6C3F1 mice of either sex.

CONTRIBUTORS

The bioassay of D-mannitol was conducted at Southern Research Institute under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The chronic study in rats was begun in April 1978 and completed in May 1980. The chronic study in mice was begun in June 1977 and completed in June 1979.

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The pathology report and selected slides were evaluated on April 12, 1981 by the NTP Pathology Working Group, which consisted of Drs. J. Ward (NCI), G. Reznik (NCI), S. Stinson (NCI), B. Gupta (NIEHS), and R. Kovatch (Tracor Jitco).

The chemicals used in this bioassay of D-mannitol were analyzed by the Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri 64110, and analysis of the formulated diets and reanalysis of the bulk chemical were performed by Southern Research Institute.

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*Unable to attend December 16, 1981 meeting

SUMMARY OF PEER REVIEW COMMENTS

On December 16, 1981, this report underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in Conference Room A, Landow Building, 7910 Woodmont Avenue, Bethesda, Maryland.

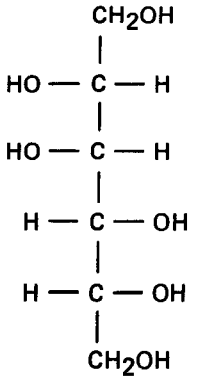
Dr. Schwetz, a principal reviewer for the report on the bioassay of D-mannitol, agreed with the conclusion that, under the conditions of this bioassay, D-mannitol was not carcinogenic for F344/N rats of B6C3F1/N mice of either sex. He commented on the finding of retinopathy and cataracts in male and female rats in the chronic study and questioned the wording of the support for the conclusion in the report that the lesions could be associated with the distance of the animals from a fluorescent light source. He said that before discharging the observation, evidence should be cited that the lesions were not related to administration of D-mannitol in the diet.

As a second principal reviewer, Dr. Vore also agreed with the conclusions of the report. She said that the highest dose used, 50,000 ppm, had little effect on survival or weight gain but was the highest concentration recommended for feeding in the bioassay program. She stated that other monosaccharides have been shown to induce cataracts and expressed concern that the degree of exposure to the fluorescent light was not controlled; this precluded interpretation or association of D-mannitol with the lesion. Dr. Mirer asked whether the induction of ocular lesions by light was dose related, and, further, whether such lesions could be distinguished from chemically-induced lesions. Dr. Schwetz replied that, in his experience, light-induced lesions were not readily distinguishable from chemical-induced lesions, nor is the onset time different.

Dr. Schwetz moved that the report on the bioassay of D-mannitol be accepted with minor changes noted in the discussion and in the reviewer's comments. Dr. Vore seconded the motion and the report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

I. INTRODUCTION



D-MANNITOL

CAS NO. 69-65-8
$C_6H_{14}O_6$ Mol. Wt. 182.17

D-Mannitol occurs in algae, fungi, bacteria, and a variety of higher plants, including pumpkins, onions, celery, strawberries, and cocoa beans (Food and Agriculture Organization, 1967; Kirk-Othmer, 1963). It is used primarily in the production of chewable tablets. Since D-mannitol has half the caloric value of glucose, it is also used as a replacement for sugar in dietary foods (Furia, 1972). Concentrations of 3%-10% D-mannitol may be found in sugarless chocolate, gum, and hard candy (Furia, 1972). Its generally recognized as safe (GRAS) status was reevaluated by the U.S. Food and Drug Administration, and it was approved subject to interim food additive regulation No. 121.4005 for use as a food additive (U.S. Code of Fed. Reg., 1976, 1977) and, as such, must be at least 96% pure (Food Chemicals Codex, 1972). The Joint FAO/WHO Expert Committee on Food Additives classified D-mannitol consumption of 50-150 mg/kg/day as "conditionally acceptable" for humans (Food and Agriculture Organization, 1967).

D-Mannitol is also used to retain moisture and give bulk to food and drugs and to improve the properties of stored products such as skim milk powder, blood, semen, and freeze-dried bacteria (Furia, 1972; Kirk - Othmer, 1978; Redway and LaPage, 1974). It is administered intravenously to humans as an osmotic diuretic (Kirk - Othmer, 1979), and is used to prevent or treat oliguria and anuria associated with major surgery (American Medical Association, 1973), to decrease intraocular pressure in patients with glaucoma (Weiss et al., 1962), and to reduce intracranial pressure (Wise and Chater, 1961).

D-Mannitol is produced commercially by the reduction of glucose or sucrose (Kirk - Othmer, 1978). Approximately 789,000 kg of D-mannitol was used in processed foods in 1970 (Life Sciences Research Office, 1972). Current production figures are not available (USITC, 1980).

The reported oral LD_{50} value is 17.3 g/kg in rats and 22 g/kg in mice (Food and Agriculture Organization, 1967). In mice, the reported LD_{50} value for D-mannitol administered intravenously is 16.8 g/kg (Food and Agriculture Organization, 1967) and for D-mannitol administered intraperitoneally is 14-16 g/kg (Beck et al., 1936).

Death in mice was preceded by central nervous system depression, damage to the gastrointestinal tract, and diarrhea (Food and Agriculture Organization, 1967).

Intravenous administration of D-mannitol (0.3 g initial dose, followed by hourly 1-g injections) to Sprague-Dawley rats resulted in complete inhibition of salt and water resorption from the medullary collecting system of the kidney (Sonnenberg, 1978). Only 1.3%-2% of the labeled carbon from [^{14}C]-D-mannitol administered by intraperitoneal injection to rats was recovered in expired carbon dioxide by 12 hours as compared with 50% for orally administered [^{14}C]-D-mannitol. This suggests that the liver plays an important role in the metabolism of this compound (Wick et al., 1954).

In humans, single oral doses greater than 20 g have a laxative effect (Ellis and Krantz,

1941). Human subjects ingesting [^{14}C]-D-mannitol eliminated 1%-7% of the label in the urine in 48 hours and 18.7% in the expired carbon dioxide in 12 hours (Nasrallah and Iber, 1969).

D-Mannitol was not mutagenic for *Salmonella typhimurium* G-46 or TA 1530 or for *Saccharomyces cerevisiae* D-3 when tested without metabolic activation (Green, 1977). Mutagenesis testing results of the National Toxicology Program at three different laboratories showed that D-mannitol was not mutagenic for *Salmonella typhimurium* TA 98, 100, 1535, and 1537 (NTP Tech. Bull., 1981).

Results of a dominant lethal assay in rats at doses of 20, 200, 2,000, and 5,000 mg/kg of D-mannitol by gavage were negative. No increases in chromosome aberrations were observed in an *in vivo* rat bone marrow study or in an *in vitro* study using WI-38 human cells (FDA, 1974).

D-Mannitol was tested for carcinogenicity because of its widespread use (as a food additive and as a medicinal) and human exposure and because of the lack of long-term carcinogenicity studies.

II. MATERIALS AND METHODS

CHEMICAL ANALYSES

PREPARATION OF TEST DIETS

PRECHRONIC STUDIES

- Single-Dose Study
- Fourteen-Day Study
- Thirteen-Week Study

CHRONIC STUDY

- Study Design
- Animal Maintenance
- Clinical Examinations and Pathology
- Data Recording and Statistical Methods

CHEMICAL ANALYSES

USP grade D-mannitol was obtained in three batches from ICI America, Atlas Chemical Division (Wilmington, DE).

Lot No. 4644 was used for the 13-week studies in rats and mice, for the first 14 months of the chronic study in mice, and for the first 2 months of the chronic study in rats. Lot No. 00041 was used for the final 10 months of the chronic study in mice and for months 3 to 6 in rats. Lot No. 20022 was used for the final 18 months of the chronic study in rats.

Purity and identity analyses were performed at Midwest Research Institute (Kansas City, MO) (Appendix E). Results of elemental analyses for carbon and hydrogen agreed with the theoretical values for all three lots. The results of titration with thiosulfate after periodate oxidation of D-mannitol indicated that Lot No. 4644 was 100.5% pure, Lot No. 00041 was 97.8% pure, and Lot No. 20022 was 99.0% pure. No impurities were detected by thin-layer chromatography in any lots. The remainder of both Lot No. 00041 and Lot No. 20022 was basically comprised of water. The ultraviolet/visible spectrum was consistent with that expected for the structure of D-mannitol. The infrared and nuclear magnetic resonance spectra were consistent with those reported in the literature.

The bulk chemical was examined at Midwest Research Institute and was found to be stable when stored at temperatures up to 60°C for 2 weeks (Appendix F). To ensure the stability of the chemical, the bioassay laboratory stored it in the dark at 5°C. Southern Research Institute analyzed each batch in use every 4 weeks throughout the study by gas chromatography after derivatization with either a silylating agent (Appendix E, Section G) or n-butane boronic acid (Appendix G) and by infrared spectroscopy. No evidence of any degradation was seen.

PREPARATION OF TEST DIETS

The feed used in the prechronic and chronic studies was ground Wayne Lab Blox® (Allied Mills, Inc., Chicago, IL). Manufacturer information indicated that the feed contained no antibiotics and that it was tested regularly to assure the absence of estrogenic activity and Salmonella. The diet composition with regard to nutritional materials was also known.

In the 14-day, 13-week, and 2-year studies, the required amount of D-mannitol was first mixed with a known amount of feed and then blended for 10 minutes (Table 1). The premix and the rest of the feed was then added to a Patterson-Kelly Twin-Shell blender and mixed for 15 minutes. This procedure was found to produce the most homogenous mixture (Appendix G). D-Mannitol mixed in feed was found to be stable for at least 2 weeks at temperatures up to 45°C. The stability of the chemical was ensured by storing formulated diets at 5°C in sealed plastic bags and using them within 2 weeks.

Samples of formulated diets used in the chronic study were periodically analyzed for concentrations of D-mannitol (Appendix H). All but five samples were within ±10% of the specified concentrations. No analyses were performed to confirm the concentrations of D-mannitol used in the 14-day or in the 13-week studies.

PRECHRONIC STUDIES

Single-Dose Study

Male and female F344/N rats and B6C3F1/N mice were obtained from Frederick Cancer Research Center and held for approximately 10 days before the study began. Rats and mice were approximately 6 weeks old when placed on study.

Animals of the same sex and species were housed five per cage in stainless steel cages. Assignments to cages and dosage groups were made according to tables of random numbers. Feed and water were available *ad libitum* during the 16-day observation period. Additional information on animal maintenance appears in Table 1.

Groups of five animals of each sex and species were administered a single dose of 300, 600, 1,200, 2,500, or 5,000 mg/kg D-mannitol in distilled water by gavage. Animals were observed twice daily for mortality and other clinical signs. No necropsies were performed.

Fourteen-Day Study

F344/N rats and B6C3F1/N mice of each sex were obtained from Frederick Cancer Research Center and held for 10 days before the study began. The animals were 6 weeks old when the study began. Animals were assigned to cages and to dosage groups according to tables of random numbers.

Groups of five males and five females of each species were fed diets containing 6,000, 12,500, 25,000, 50,000, or 100,000 ppm D-mannitol for 14 days (Table 1). No control groups were used. Animals were observed twice daily for mortality and were weighed on days 1 and 15. Animals were killed on days 16 to 20, and necropsies were performed on all animals.

Thirteen-Week Study

Thirteen-week studies were conducted to evaluate the cumulative toxicity of D-mannitol and to determine the concentrations to be used in the chronic studies.

Four-week-old male and female F344/N rats and B6C3F1/N mice were obtained from the Frederick Cancer Research Center and observed for 6 days. Animals of the same sex and species were housed five per cage in stainless steel cages. The animals were assigned to cages and dosage groups according to tables of random numbers. Ten rats and 10 mice of each sex were fed *ad libitum* diets containing 0, 3,000, 6,000, 12,500, 25,000, or 50,000 ppm D-mannitol for 13 weeks. [Male and female rats and mice in the 3,000-and 6,000-ppm groups accidentally received diets containing 3,000 or 6,000 ppm ziram (CAS No. 137-30-4) for one day (day 56).] Environmental conditions and animal maintenance procedures are described in Table 1.

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 weekly clinical examination which included 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, and necropsies were performed on animals that survived to the end of the study and on all dead animals not autolyzed or cannibalized.

The following tissues were examined for control, 25,000-ppm, and 50,000-ppm groups: peripheral blood, skin, lymph nodes, mammary glands, skeletal muscles, bone marrow, thymus, larynx, trachea, heart, thyroid, lung, parathyroid, esophagus, stomach, small intestine, colon, liver, pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles, prostate, testes, uterus, ovaries, brain, and pituitary. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

CHRONIC STUDY

Study Design

Three- to four-week-old male and female F344/N rats were obtained from Harlan Industries, Inc. and observed for 13 days before being placed on study (Table 1). Four-week-old male and female B6C3F1/N mice were obtained from the NCI Frederick Cancer Research Center and observed for 7 days before being placed on study. The initial weights of animals used in the study were: male rats, 82-128 g; female rats, 70-120 g; male mice, 13-25 g; and female mice, 13-20 g. Only those animals that appeared healthy were used for the study.

Fifty male and 50 female rats and a similar number of male and female mice were fed diets containing 0, 25,000, or 50,000 ppm D-mannitol for 103 weeks. The assignment of animals to dosage groups was done according to tables of random numbers.

Animal Maintenance

Animals of the same sex and species were housed in groups of five in polycarbonate cages. Distribution of animals to cages was done according to a table of random numbers. Bedding and cages were changed twice weekly and racks and filters were changed once every 2 weeks. Tap water was offered via an automatic watering system. Experimental diets were offered *ad libitum* for 103 weeks. The animal room temperature was 20°-24°C with 30%-60% relative humidity. Room air underwent 15 changes per hour. Fluorescent light illumination was provided 12 hours per day. No other chemicals were on test in the same room with rats used for the D-mannitol study. However, mice used in this study were housed with mice fed eugenol (CAS No. 97-53-0) for the first year and with mice fed ziram (CAS No. 137-30-4) for the entire study period.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of toxicity. Clinical signs were recorded monthly. Body weights and feed consumption by cage were recorded at least every 4 weeks. 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 with carbon dioxide and necropsied at weeks 104-106.

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. Special staining techniques were used as necessary. Tissues examined microscopically are listed in Table 1.

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 pathology report and selected slides were evaluated by the NTP Pathology Working Group as described by Ward et al. (1978). Neoplastic nodules were classified according to the recommendations of Squire and Levitt (1975) and the National Academy of Sciences (1980). The diagnoses represent a consensus of contracting 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 (1958) 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.

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 for significance included pairwise comparisons of high-and low-dose 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. The results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel methods 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 are one-sided.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses are usually similar. When differing results are obtained by the three methods, the final interpretation of the data depends 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 OF PRECHRONIC AND CHRONIC STUDIES OF RATS AND MICE FED DIETS CONTAINING D-MANNITOL

	Single-Dose	14-Day Study	13-Week Study	Chronic Study
Experimental Design				
Size of Test Groups	5 males and 5 females of each species	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	300, 600, 1,200, 2,500, or 5,000 mg/kg D-mannitol in distilled water by gavage	6,000, 12,500, 25,000, 50,000, or 100,000 ppm D-mannitol in feed; available *ad libitum*	0, 3,000, 6,000, 12,500, 25,000, or 50,000 ppm D-mannitol in feed; available *ad libitum*	0, 25,000, or 50,000 ppm D-mannitol in feed; available *ad libitum*
Duration of Dosing	Single dose; killed day 16	14 days; killed days 16 to 20	13 weeks; killed days 92 to 99	103 weeks; killed weeks 104 to 106
Type and Frequency of Observation	Observed twice daily for mortality	Observed twice daily for mortality and weighed on days 1 and 15.	Observed twice daily; weighed once per week	Observed twice daily; weighed every 4 weeks
Necropsy and Histologic Examination	None performed	All animals necropsied	All animals necropsied; controls and test groups receiving 25,000 ppm and 50,000 ppm received histopathologic examination *(a)*	All animals necropsied and examined histologically *(b)*
Animals and Animal Maintenance				
Species	F344/N rats; B6C3F1/N mice	F344/N rats; B6C3F1/N mice	F334/N rats; B6C3F1/N mice	F344/N rats; B6C3F1/N mice
Animal Source	Frederick Cancer Research Center (Frederick, MD)	Frederick Cancer Research Center (Frederick, MD)	Frederick Cancer Research Center (Frederick, MD)	Rats: Harlan Industries (Indianapolis, IN) Mice: Frederick Cancer Research Center (Frederick, MD)
Time Held Before Start of Test	10 days	10 days	6 days	Rats: 13 days Mice: 7 days
Age When Placed on Study	6 weeks	6 weeks	5 weeks	Rats: 36 days old Mice: 40 days old

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS OF PRECHRONIC AND CHRONIC STUDIES OF RATS AND MICE FED DIETS CONTAINING D-MANNITOL (Continued)

	Single-Dose	14-Day Study	13-Week Study	Chronic Study
Method of Animal Distribution	Assigned to cages according to a table of random numbers, then to dosed groups according to a second table of random numbers	Same as single-dose study	Same as single-dose study	Same as single-dose study
Feed	Wayne Lab Blox® Allied Mills, Inc. (Chicago, IL); available *ad libitum*	Same as single-dose study	Same as single-dose study; hoppers changed once a week	Same as single-dose study; hoppers changed once a week
Bedding	Heat-treated hardwood chips, Beta-Chips® Northeastern Products Corp. (Warrensburg, NY)	Same as single-dose study	Same as single-dose study; bedding replaced twice weekly	Same as single-dose study *(c)*; bedding replaced twice weekly
Water	Tap water in bottles available *ad libitum*	Same as single-dose study	Same as single-dose study; bottles replaced once a week	Automatic Watering System, Edstrom Industries, Inc. (Waterford, WI)
Cages	Stainless steel, Hahn Roofing and Sheet Metal Co. (Birmingham, AL)	Same as single-dose study	Same as single-dose study; cages replaced once a week.	Polycarbonate, Lab Products, Inc. (Garfield, NJ) Cages replaced twice weekly.
Cage Filters	Filter Bonnets	Same as single-dose study	Same as single-dose study; Racks and filters changed once every 2 weeks.	Spun-bonded polyester filters. Racks and filters changed once every 2 weeks.
Animals per Cage	5	5	5	5

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS OF PRECHRONIC AND CHRONIC STUDIES OF RATS AND MICE FED DIETS CONTAINING D-MANNITOL (Continued)

	Single-Dose	14-Day Study	13-Week Study	Chronic Study
Animal Room Environment	20°-24°C; 30%-60% relative humidity, room air changed 15 times per hour, 9 hours of fluorescent light	Same as single-dose study	Same as single-dose study	20°-24°C; 30%-60% relative humidity, room air changed 15 times per hour, 12 hours of fluorescent light per day
Other Chemicals on Test in the Same Room			Stannous chloride, ziram, ethyl acrylate, eugenol, allyl isothiocyanate, propyl gallate, zearalenone	Rats: none Mice: eugenol (first year) ziram (entire test period)
Chemical Feed Mixture Preparation	Weighed portion of D-mannitol added to distilled water; mixture heated (110°F) until dissolved	Weighed portion of D-mannitol for each dose level was sifted, then mixed with small amount (1 cup) Wayne Lab Blox® mash. Mixture was blended in Hamilton Beach Mixmaster until uniform. This mixture was added to remaining mash and mixed in a Patterson-Kelly® Twin Shell Blender for 15 min.	Same as 14-day study	Weighed portion of D-mannitol for each dose level was mixed with portion of Wayne Lab Blox® mash. Mixture was blended in Patterson-Kelly® Twin Shell Blender for 10 min. Remainder of allotted feed was then added to blender and mixed additional 15 min.
Maximum Storage Time		7 days	14 days	14 days
Storage Conditions		Sealed plastic bags; 5°C	Same as 14-day study	Same as 14-day study

(a) The following tissues were examined: peripheral blood, skin, lymph nodes, mammary glands, salivary glands, skeletal muscles, bone marrow, thymus, larynx, lung, trachea, heart, thyroids, parathyroids, esophagus, stomach, small intestines, colon, liver, pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles, uterus, ovary, prostate, testes, brain, and pituitary.

(b) The following tissues were examined: pituitary, abnormal lymph nodes, tissue masses, brain, eyes, external and middle ear, spinal cord, mandibular lymph node, nasal cavity, thyroid, parathyroids, salivary glands, thymus, larynx, heart, liver, gall bladder, pancreas, spleen, adrenals, kidneys, urinary bladder, inguinal lymph node, mesenteric lymph node, mammary gland, sciatic nerve, bone (femur), trachea, esophagus, lungs, bronchi, costochondral junction, (rib), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, bone marrow (femoral), thigh muscle, ovaries, fallopian tubes, uterus, vagina, seminal vesicles, prostate, testes, epididymis, skin (abdominal).

(c) In the mouse study the bedding was changed to sawdust (P.W.I., Inc.; Lowville, N.Y.) for days 234-344, 371-555, and 620-630. In the rat study sawdust was used for days 1-177 and 242-252.

III. RESULTS

RATS

PRECHRONIC STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

CHRONIC STUDY

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

PRECHRONIC STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

CHRONIC STUDY

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

PRECHRONIC STUDIES

Single-Dose Study

Rats were observed for 15 days. All animals survived to the end of the 16-day test period. No compound-related effects were observed. Because of these findings, dose levels of 6,000, 12,500, 25,000, 50,000, and 100,000 ppm were selected for the 14-day study. The 100,000-ppm dose level was selected so that the effects of doses above and below 50,000 ppm could be examined.

Fourteen-Day Study

All animals survived to the end of the dosing period (Table 2). Females fed diets containing 100,000 ppm gained less weight than did other groups of dosed females. Two of the five male rats administered the 100,000-ppm diets had diarrhea from days 4 to 6. No gross lesions were observed at necropsy. The dose levels selected for the 13-week study were 0, 3,000, 6,000, 12,500, 25,000, and 50,000 ppm D-mannitol in the diet.

TABLE 2. DOSAGE, SURVIVAL, AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING D-MANNITOL FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)		
		Initial	Final	Change
Males				
6,000	5/5	80	138	+ 58
12,500	5/5	89	144	+ 55
25,000	5/5	94	139	+ 45
50,000	5/5	87	131	+ 44
100,000	5/5	84	135	+ 51
Females				
6,000	5/5	80	120	+ 40
12,500	5/5	84	111	+ 27
25,000	5/5	76	107	+ 31
50,000	5/5	84	112	+ 28
100,000	5/5	80	101	+ 21

(a) Number surviving/number initially in the group.

Thirteen-Week Study

All animals survived. Mean body weight gain of males administered diets containing 50,000 ppm D-mannitol was depressed 9.6% relative to controls; mean body weight gains of other dosed groups were approximately the same as those of controls (Table 3). No compound-related clinical signs or histopathologic effects were observed. The principal histopathologic findings in the control, 25,000-ppm, and 50,000-ppm groups were mild to moderate peribronchial lymphoid hyperplasia and cystic ovaries. These changes did not appear to be related to administration of D-mannitol and were considered to be incidental.

Doses of 25,000 and 50,000 ppm D-mannitol in the diet were selected for rats in the chronic study because the latter dose is the maximum concentration recommended for chronic feeding studies (NCI, 1976).

TABLE 3. DOSAGE, SURVIVAL, AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING D-MANNITOL FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Change Relative to Controls *(c)* (Percent)	Average Daily Feed Consumption (grams)
		Initial	Final	Change *(b)*		
Males						
0	10/10	73.3 ± 3.0	304.4 ± 5.9	+231.1 ± 4.4		13.7
3,000	10/10	70.3 ± 2.3	296.7 ± 4.9	+226.4 ± 5.0	- 2.0	15.5
6,000	10/10	66.1 ± 1.7	293.9 ± 3.0	+227.8 ± 4.0	- 1.4	15.2
12,500	10/10	73.5 ± 3.8	306.9 ± 4.9	+233.4 ± 2.0	+ 1.0	15.5
25,000	10/10	71.2 ± 2.5	302.1 ± 5.6	+230.9 ± 5.0	- 0.1	15.4
50,000	10/10	74.6 ± 2.6	283.6 ± 4.8	+209.0 ± 4.8	- 9.6	16.1
Females						
0	10/10	68.9 ± 2.8	183.3 ± 3.1	+114.4 ± 3.0		10.9
3,000	10/10	63.7 ± 1.9	178.6 ± 2.5	+114.9 ± 2.4	+ 0.4	10.8
6,000	10/10	67.1 ± 3.0	184.7 ± 3.6	+117.6 ± 2.9	+ 2.8	10.5
12,500	10/10	64.1 ± 1.9	182.9 ± 3.4	+118.8 ± 4.1	+ 3.8	11.0
25,000	10/10	66.3 ± 2.8	184.8 ± 4.3	+118.5 ± 2.7	+ 3.6	10.9
50,000	10/10	62.1 ± 2.5	173.6 ± 3.3	+111.5 ± 3.8	- 2.5	10.4

(a) Number surviving/number initially in the group.

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

(c) Weight change of the dosed group relative to that of the controls ▫

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

Body Weights and Clinical Signs

Mean body weights of dosed and control male rats were comparable throughout the study; those for dosed female rats were slightly lower than control values during most of the study period (Figure 1 and Table 4). The average daily feed consumption for low- and high-dose rats compared with controls was 108% (16.6/15.4) and 102% (15.7/15.4) that of controls for males, and 99% (11.3/11.4) and 96% (10.9/11.4) for females (Appendix I, Table I1).

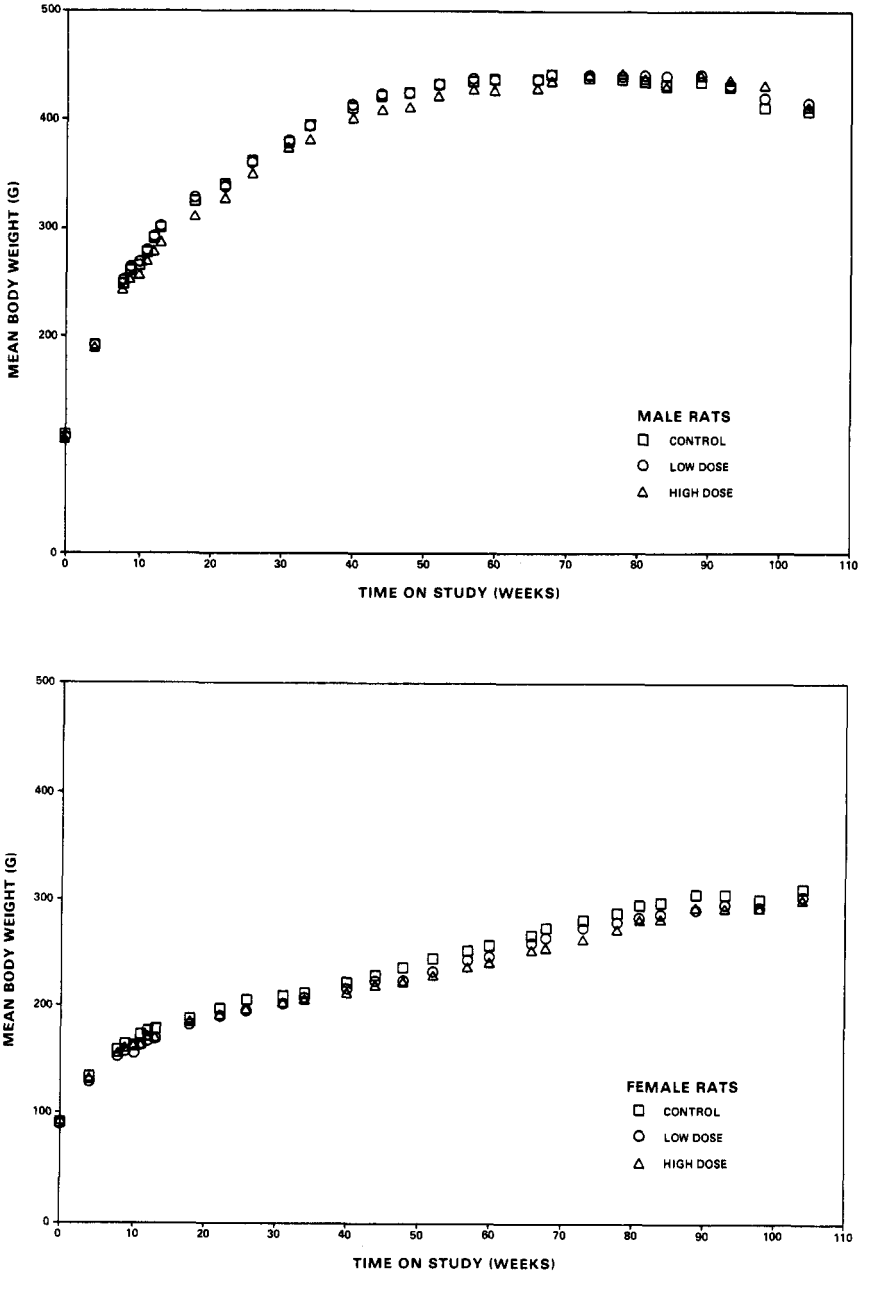


Figure 1. Growth Curves for Rats Fed Diets Containing D-Mannitol

TABLE 4. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF RATS FED DIETS CONTAINING D-MANNITOL IN THE CHRONIC STUDY

	Cumulative Mean Body Weight Change (grams)			Weight Change Relative to Controls *(a)* (Percent)	
Week	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
0	106 *(b)*	105 *(b)*	103 *(b)*		
4	84	85	84	+ 1	0
26	256	255	247	0	- 4
48	318	319	308	0	- 3
68	335	336	332	0	- 1
89	329	336	336	+ 2	+ 2
104	302	311	309	+ 3	+ 2
Females					
0	91 *(b)*	90 *(b)*	92 *(b)*		
4	42	38	38	-10	-10
26	114	104	103	- 9	-10
48	145	134	131	- 8	-10
68	182	174	163	- 4	-10
89	215	201	200	- 7	- 7
104	220	214	208	- 3	- 5

(a) Weight change of the dosed group relative to that of the controls =

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

(b) Initial Weight

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing D-mannitol at the concentrations used in this bioassay, and those for the control groups, are shown by the Kaplan and Meier curves in Figure 2. The incidence of surviving high-dose female rats was significantly greater (P=0.018) than that of low-dose females. No other significant differences in survival were observed.

In male rats, 32/50 (64%) of the controls, 36/50 (72%) of the low-dose group, and 32/50 (64%) of the high-dose group lived to the end of the study at 104-106 weeks. In female rats, 36/50 (72%) of the controls, 32/50 (64%) of the low-dose group, and 42/50 (84%) of the high-dose group lived to the end of the study. These incidences include as survivors three control males, one high-dose male, and two low-dose females that died during the termination of the study; for statistical purposes, these animals were considered as killed during this period.

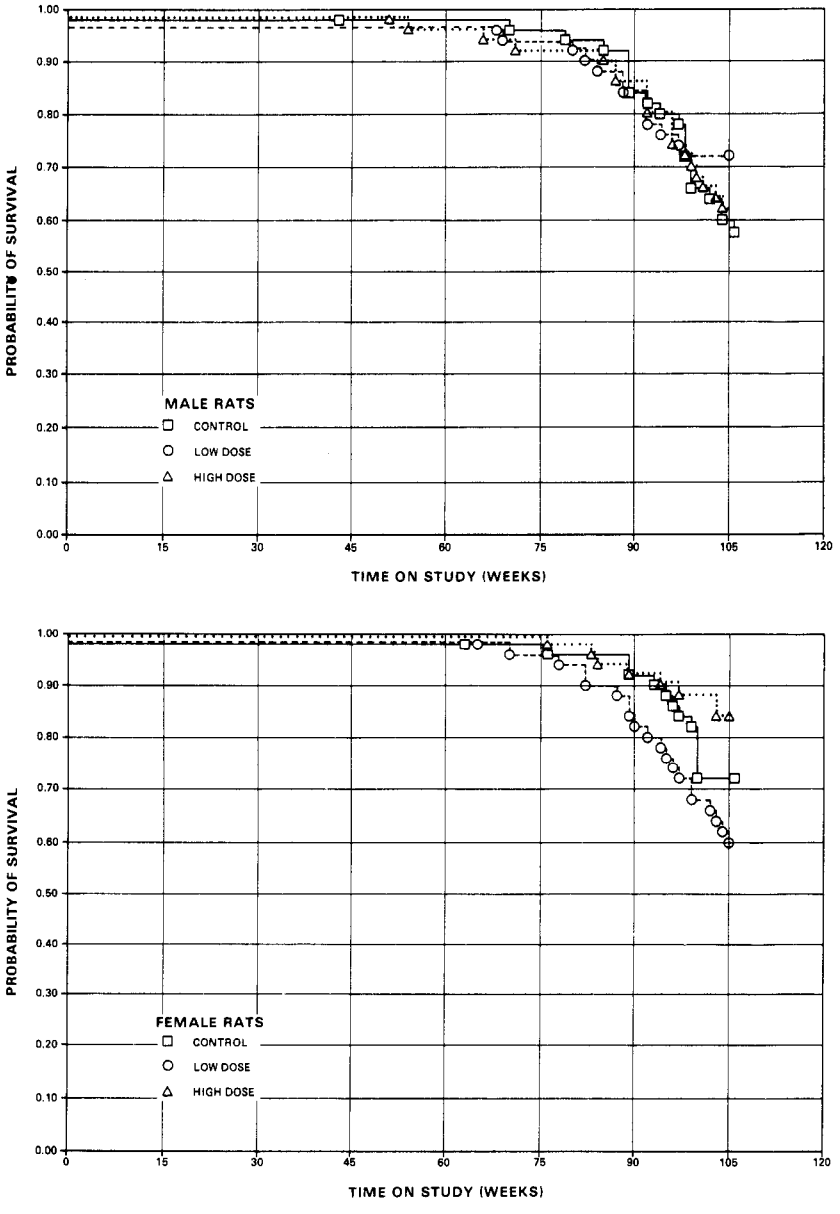


Figure 2. Survival Curves for Rats Fed Diets Containing D-Mannitol

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 individual animal in the male and female rat studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Tables 5 and 6 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Eye: Retinopathy and cataracts occurred at increased incidences in high-dose male rats and dosed female rats (retinopathy: males—17/50, 6/50, 42/50; females—10/50, 43/50, 33/50; cataracts: males—15/50, 6/50, 40/50; females—9/50, 40/50, 32/50). This increase appears to be associated with the distance of the animals from sources of fluorescent light; yet a contributing effect of D-mannitol cannot be discounted completely.

Stomach: Dilatation of the gastric fundal gland was observed at increased incidences in dosed females (control, 6/50, 12%; low-dose, 23/50, 46%; high-dose, 23/50, 46%).

No statistically significant incidences of tumors were observed at any site in rats of either sex.

TABLE 5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)*

	Control	Low Dose	High Dose
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	3/50 (6%)	5/50 (10%)
Adjusted *(c)*	6.3%	8.3%	14.5%
Terminal *(d)*	2/32 (6%)	3/36 (8%)	4/32 (13%)
Statistical Tests *(e)*			
Life Table	P=0.154	P=0.554	P=0.218
Incidental Tumor Test	P=0.148	P=0.554	P=0.208
Cochran-Armitage Trend, Fisher Exact Tests	P=0.159	P=0.500	P=0.218
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted *(c)*	0.0%	8.3%	6.3%
Terminal *(d)*	0/32 (0%)	3/36 (8%)	2/32 (6%)
Statistical Tests *(e)*			
Life Table	P=0.196	P=0.142	P=0.238
Incidental Tumor Test	P=0.196	P=0.142	P=0.238
Cochran-Armitage Trend, Fisher Exact Tests	P=0.203	P=0.121	P=0.247
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall *(b)*	13/50 (26%)	14/50 (28%)	11/50 (22%)
Adjusted *(c)*	30.9%	33.3%	27.2%
Terminal *(d)*	5/32 (16%)	9/36 (25%)	4/32 (13%)
Statistical Tests *(e)*			
Life Table	P=0.391N	P=0.549	P=0.428N
Incidental Tumor Test	P=0.420N	P=0.383	P=0.499N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.365N	P=0.500	P=0.408N
Hematopoietic System: Leukemia			
Tumor Rates			
Overall *(b)*	14/50 (28%)	14/50 (28%)	11/50 (22%)
Adjusted *(c)*	33.4%	33.3%	27.2%
Terminal *(d)*	6/32 (19%)	9/36 (25%)	4/32 (13%)
Statistical Tests *(e)*			
Life Table	P=0.314N	P=0.527N	P=0.350N
Incidental Tumor Test	P=0.331N	P=0.480	P=0.402N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.285N	P=0.588	P=0.322N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	16/50 (32%)	14/50 (28%)	11/50 (22%)
Adjusted *(c)*	37.3%	33.3%	27.2%
Terminal *(d)*	7/32 (22%)	9/36 (25%)	4/32 (13%)
Statistical Tests *(e)*			
Life Table	P=0.190N	P=0.368N	P=0.220N
Incidental Tumor Test	P=0.191N	P=0.576	P=0.240N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.157N	P=0.414N	P=0.184N

TABLE 5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	9/46 (20%)	10/50 (20%)	8/50 (16%)
Adjusted *(c)*	25.5%	24.0%	21.5%
Terminal *(d)*	6/30 (20%)	6/36 (17%)	4/32 (13%)
Statistical Tests *(e)*			
Life Table	P=0.428N	P=0.592	P=0.473N
Incidental Tumor Test	P=0.394N	P=0.550N	P=0.478N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.372N	P=0.581	P=0.424N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	14/50 (28%)	10/50 (20%)	9/50 (18%)
Adjusted *(c)*	36.8%	27.8%	25.6%
Terminal *(d)*	9/32 (28%)	10/36 (28%)	7/32 (22%)
Statistical Tests *(e)*			
Life Table	P=0.142N	P=0.176N	P=0.186N
Incidental Tumor Test	P=0.157N	P=0.255N	P=0.202N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.140N	P=0.241N	P=0.171N
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	8/49 (16%)	4/50 (8%)	5/50 (10%)
Adjusted *(c)*	23.0%	10.4%	15.6%
Terminal *(d)*	6/32 (19%)	3/36 (8%)	5/32 (16%)
Statistical Tests *(e)*			
Life Table	P=0.217N	P=0.146N	P=0.279N
Incidental Tumor Test	P=0.219N	P=0.202N	P=0.274N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.205N	P=0.168N	P=0.264N
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	10/49 (20%)	5/50 (10%)	6/50 (12%)
Adjusted *(c)*	28.2%	12.5%	18.8%
Terminal *(d)*	7/32 (22%)	3/36 (8%)	6/32 (19%)
Statistical Tests *(e)*			
Life Table	P=0.159N	P=0.107N	P=0.210N
Incidental Tumor Test	P=0.164N	P=0.170N	P=0.204N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.148N	P=0.122N	P=0.194N
Pancreatic Islets: Islet-Cell Adenoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	3/50 (6%)	4/50 (8%)
Adjusted *(c)*	8.5%	8.3%	11.3%
Terminal *(d)*	2/32 (6%)	3/36 (8%)	3/32 (9%)
Statistical Tests *(e)*			
Life Table	P=0.418	P=0.620N	P=0.496
Incidental Tumor Test	P=0.405	P=0.633	P=0.479
Cochran-Armitage Trend, Fisher Exact Tests	P=0.421	P=0.661	P=0.500

TABLE 5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Testis: Interstitial-Cell Tumor			
Tumor Rates			
Overall *(b)*	45/50 (90%)	44/50 (88%)	45/50 (90%)
Adjusted *(c)*	95.7%	97.8%	100.0%
Terminal *(d)*	30/32 (94%)	35/36 (97%)	32/32 (100%)
Statistical Tests *(e)*			
Life Table	P=0.522	P=0.252N	P=0.558
Incidental Tumor Test	P=0.397	P=0.642N	P=0.545
Cochran-Armitage Trend, Fisher Exact Tests	P=0.564	P=0.500N	P=0.630
Zymbal's Gland: Squamous Cell Carcinoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted *(c)*	8.1%	4.9%	0.0%
Terminal *(d)*	1/32 (3%)	1/36 (3%)	0/32 (0%)
Statistical Tests *(e)*			
Life Table	P=0.085N	P=0.485N	P=0.126N
Incidental Tumor Test	P=0.104N	P=0.653N	P=0.133N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.083N	P=0.500N	P=0.121N

(a) Dosed groups received doses of 25,000 or 50,000 ppm of D-mannitol 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 nonfatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

TABLE 6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)*

	Control	Low Dose	High Dose
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall *(b)*	10/50 (20%)	8/50 (16%)	4/50 (8%)
Adjusted *(c)*	25.1%	18.6%	8.9%
Terminal *(d)*	7/36 (19%)	2/32 (6%)	2/42 (5%)
Statistical Tests *(e)*			
Life Table	P=0.051N	P=0.499N	P=0.052N
Incidental Tumor Test	P=0.097N	P=0.353N	P=0.109N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.061N	P=0.398N	P=0.074N
Hematopoietic System: Leukemia			
Tumor Rates			
Overall *(b)*	10/50 (20%)	8/50 (16%)	5/50 (10%)
Adjusted *(c)*	25.1%	18.6%	11.2%
Terminal *(d)*	7/36 (19%)	2/32 (6%)	3/42 (7%)
Statistical Tests *(e)*			
Life Table	P=0.087N	P=0.499N	P=0.092N
Incidental Tumor Test	P=0.160N	P=0.353N	P=0.176N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.107N	P=0.398N	P=0.131N
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	24/50 (48%)	15/47 (32%)	19/48 (40%)
Adjusted *(c)*	53.7%	41.8%	41.7%
Terminal *(d)*	16/36 (44%)	11/31 (35%)	14/40 (35%)
Statistical Tests *(e)*			
Life Table	P=0.127N	P=0.162N	P=0.149N
Incidental Tumor Test	P=0.259N	P=0.082N	P=0.334N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.224N	P=0.079N	P=0.263N
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	25/50 (50%)	17/47 (36%)	19/48 (40%)
Adjusted *(c)*	56.0%	44.2%	41.7%
Terminal *(d)*	17/36 (47%)	11/31 (35%)	14/40 (35%)
Statistical Tests *(e)*			
Life Table	P=0.097N	P=0.227N	P=0.110N
Incidental Tumor Test	P=0.201N	P=0.096N	P=0.260N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.171N	P=0.121N	P=0.202N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall (b)	2/49 (4%)	3/50 (6%)	1/50 (2%)
Adjusted (c)	5.7%	8.9%	2.4%
Terminal (d)	2/35 (6%)	2/32 (6%)	1/42 (2%)
Statistical Tests *(e)*			
Life Table	P=0.339N	P=0.454	P=0.437N
Incidental Tumor Test	P=0.391N	P=0.448	P=0.437N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.392N	P=0.510	P=0.492N

TABLE 6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Adrenal: Cortical Adenoma			
Tumor Rates			
Overall *(b)*	1/49 (2%)	4/50 (8%)	2/50 (4%)
Adjusted *(c)*	2.9%	12.5%	4.8%
Terminal *(d)*	1/35 (3%)	4/32 (13%)	2/42 (5%)
Statistical Tests *(e)*			
Life Table	P=0.491	P=0.152	P=0.563
Incidental Tumor Test	P=0.491	P=0.152	P=0.563
Cochran-Armitage Trend, Fisher Exact Tests	P=0.415	P=0.187	P=0.508
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	6/50 (12%)	6/50 (12%)	3/50 (6%)
Adjusted *(c)*	15.4%	17.3%	7.1%
Terminal *(d)*	4/36 (11%)	4/32 (13%)	3/42 (7%)
Statistical Tests *(e)*			
Life Table	P=0.152N	P=0.529	P=0.184N
Incidental Tumor Test	P=0.251N	P=0.510	P=0.275N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.203N	P=0.620	P=0.243N
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	6/50 (12%)	8/50 (16%)	4/50 (8%)
Adjusted *(c)*	15.4%	23.2%	9.5%
Terminal *(d)*	4/36 (11%)	6/32 (19%)	4/42 (10%)
Statistical Tests (e)			
Life Table	P=0.240N	P=0.298	P=0.289N
Incidental Tumor Test	P=0.359N	P=0.277	P=0.399N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.323N	P=0.387	P=0.370N
Mammary Gland: Adenocarcinoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted *(c)*	7.7%	9.1%	0.0%
Terminal *(d)*	2/36 (6%)	2/32 (6%)	0/42 (0%)
Statistical Tests *(e)*			
Life Table	P=0.085N	P=0.606	P=0.104N
Incidental Tumor Test	P=0.133N	P=0.590	P=0.151N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.102N	P=0.661	P=0.121N
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(b)*	10/50 (20%)	14/50 (28%)	7/50 (14%)
Adjusted *(c)*	24.1%	38.0%	16.7%
Terminal *(d)*	6/36 (17%)	10/32 (31%)	7/42 (17%)
Statistical Tests *(e)*			
Life Table	P=0.184N	P=0.163	P=0.214N
Incidental Tumor Test	P=0.316N	P=0.160	P=0.363N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.269N	P=0.241	P=0.298N

TABLE 6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(b)*	10/50 (20%)	5/50 (10%)	11/50 (22%)
Adjusted *(c)*	25.0%	14.9%	25.4%
Terminal *(d)*	7/36 (19%)	4/32 (13%)	10/42 (24%)
Statistical Tests *(e)*			
Life Table	P=0.529N	P=0.204N	P=0.559N
Incidental Tumor Test	P=0.462	P=0.206N	P=0.522
Cochran-Armitage Trend, Fisher Exact Tests	P=0.448	P=0.131N	P=0.500
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(b)*	10/50 (20%)	7/50 (14%)	11/50 (22%)
Adjusted *(c)*	25.0%	19.0%	25.4%
Terminal *(d)*	7/36 (19%)	4/32 (13%)	10/42 (24%)
Statistical Tests *(e)*			
Life Table	P=0.528N	P=0.409N	P=0.559N
Incidental Tumor Test	P=0.444	P=0.358N	P=0.522
Cochran-Armitage Trend, Fisher Exact Tests	P=0.449	P=0.298N	P=0.500

(a) Dosed groups received doses of 25,000 or 50,000 ppm of D-mannitol 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 nonfatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

PRECHRONIC STUDIES

Single-Dose Study

All animals survived to the end of the 16-day observation period. No compound-related effects were observed. Based on the results of this study, levels of 6,000, 12,500, 25,000, 50,000, and 100,000 ppm were chosen for the 14-day study. The 100,000-ppm dose level was selected so that the effects of doses above and below 50,000 ppm could be examined.

Fourteen-Day Study

All animals survived to the end of the dosing period (Table 7). All groups of mice had similar increases in body weight. No compound-related effects were observed. The dose levels selected for the 13-week study were 0, 3,000, 6,000, 12,500, 25,000, and 50,000 ppm D-mannitol in the diet.

TABLE 7. DOSAGE, SURVIVAL, AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING D-MANNITOL FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)		
		Initial	Final	Change
Males				
6,000	5/5	20	25	+5
12,500	5/5	20	25	+5
25,000	5/5	19	24	+5
50,000	5/5	21	25	+4
100,000	5/5	20	25	+5
Females				
6,000	5/5	16	18	+2
12,500	5/5	17	20	+3
25,000	5/5	16	19	+3
50,000	5/5	16	19	+3
100,000	5/5	15	19	+4

(a) Number surviving/number initially in the group.

Thirteen-Week Study

All mice survived. Feed consumption for dosed and control mice was approximately the same. Increases in mean body weight were higher in dosed mice of each sex than in controls, except for male mice receiving 50,000 ppm D-manitol in the diet. These mice had 0.8% depression in body weight gain relative to controls (Table 8). No compound-related effects were observed at necropsy or during histopathologic examination.

Doses selected for mice in the chronic study were 25,000 and 50,000 ppm D-mannitol in feed, the latter being the maximum concentration recommended for chronic feeding studies (NCI, 1976).

TABLE 8. DOSAGE, SURVIVAL, AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING D-MANNITOL FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Change Relative to Controls *(c)* (Percent)	Average Daily Feed Consumption (grams)
		Initial	Final	Change *(b)*		
Males						
0	10/10	19.3 ± 0.6	+31.5 ± 0.6	+12.2 ± 0.5		10.8
3,000	10/10	19.5 ± 0.7	+31.9 ± 0.7	+12.4 ± 0.5	+ 1.6	10.7
6,000	10/10	19.1 ± 0.4	+31.6 ± 0.3	+12.5 ± 0.5	+ 2.5	10.8
12,500	10/10	18.7 ± 0.6	+31.6 ± 0.8	+12.9 ± 0.7	+ 5.7	10.4
25,000	10/10	19.3 ± 0.4	+32.3 ± 0.7	+13.0 ± 0.6	+ 6.6	10.6
50,000	10/10	19.0 ± 0.5	+31.1 ± 0.8	+12.1 ± 0.5	- 0.8	10.5
Females						
0	10/10	15.9 ± 0.4	+23.7 ± 0.5	+ 7.8 ± 0.1		10.2
3,000	10/10	15.9 ± 0.4	+24.6 ± 0.3	+ 8.7 ± 0.4	+11.5	10.2
6,000	10/10	15.8 ± 0.4	+24.5 ± 0.5	+ 8.7 ± 0.5	+11.5	10.0
12,500	10/10	16.0 ± 0.3	+24.9 ± 0.5	+ 8.9 ± 0.4	+14.1	9.5
25,000	10/10	17.5 ± 0.5	+25.6 ± 0.4	+ 8.1 ± 0.5	+ 3.8	10.3
50,000	10/10	16.1 ± 0.3	+24.7 ± 0.5	+ 8.6 ± 0.5	+10.3	10.1

(a) Number surviving/number initially in the group.

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

(c) Weight change of the dosed group relative to that of the controls =

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

CHRONIC STUDY

Body Weights and Clinical Signs

Mean body weights of dosed and control mice of each sex were similar (Figure 3 and Table 9). The average daily feed consumption by individual low- and high-dose mice was 100% (8.1/8.1) and 99% (8.0/8.1) that of controls for males and 95% (7.9/8.3) and 98% (8.1/8.3) for females (Appendix I, Table 12). No compound-related clinical signs were observed.

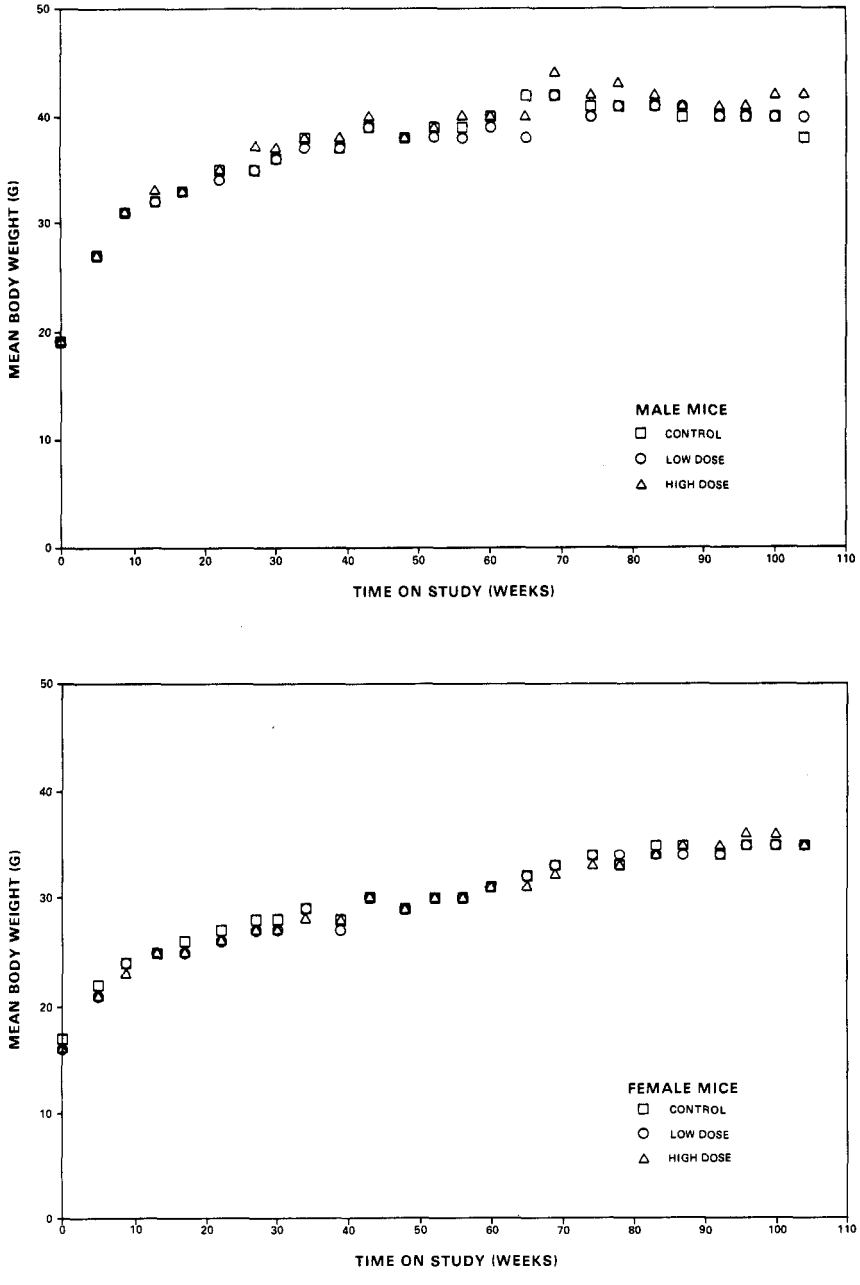


Figure 3. Growth Curves for Mice Fed Diets Containing D-Mannitol

TABLE 9. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF MICE FED DIETS CONTAINING D-MANNITOL IN THE CHRONIC STUDY

Week	Cumulative Mean Body Weight Change (grams)			Weight Change Relative to Controls *(a)* (Percent)	
	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
0	19 *(b)*	19 *(b)*	19 *(b)*		
5	8	8	8	0	0
27	16	16	18	0	+13
48	19	19	19	0	0
69	23	23	25	0	+ 9
87	21	22	22	+ 5	+ 5
104	19	21	23	+11	+21
Females					
0	17 *(b)*	16 *(b)*	16 *(b)*		
5	5	5	5	0	0
27	11	11	11	0	0
48	12	13	13	+ 8	+ 8
69	16	17	16	+ 6	0
87	18	18	19	0	+ 6
104	18	19	19	+ 6	+ 6

(a) Weight change of the dosed group relative to that of the controls =

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

(b) Initial Weight

Survival

Estimates of the probabilities of survival of male and female mice fed diets containing D-mannitol at the concentrations used in this bioassay and those of the control groups are shown by the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of males or females.

In male mice, 39/50 (78%) of the controls, 43/50 (86%) of the low-dose group, and 41/50 (82%) of the high-dose group lived to the termination period of the study at 104-106 weeks. In female mice, 37/50 (74%) of the controls, 38/50 (76%) of the low-dose group, and 34/50 (68%) of the high-dose group lived to the termination period of the study at 104-106 weeks. These incidences include as survivors one male and two female control mice that died during the terminal kill period. For statistical purposes, these three animals are considered to have been killed during this period.

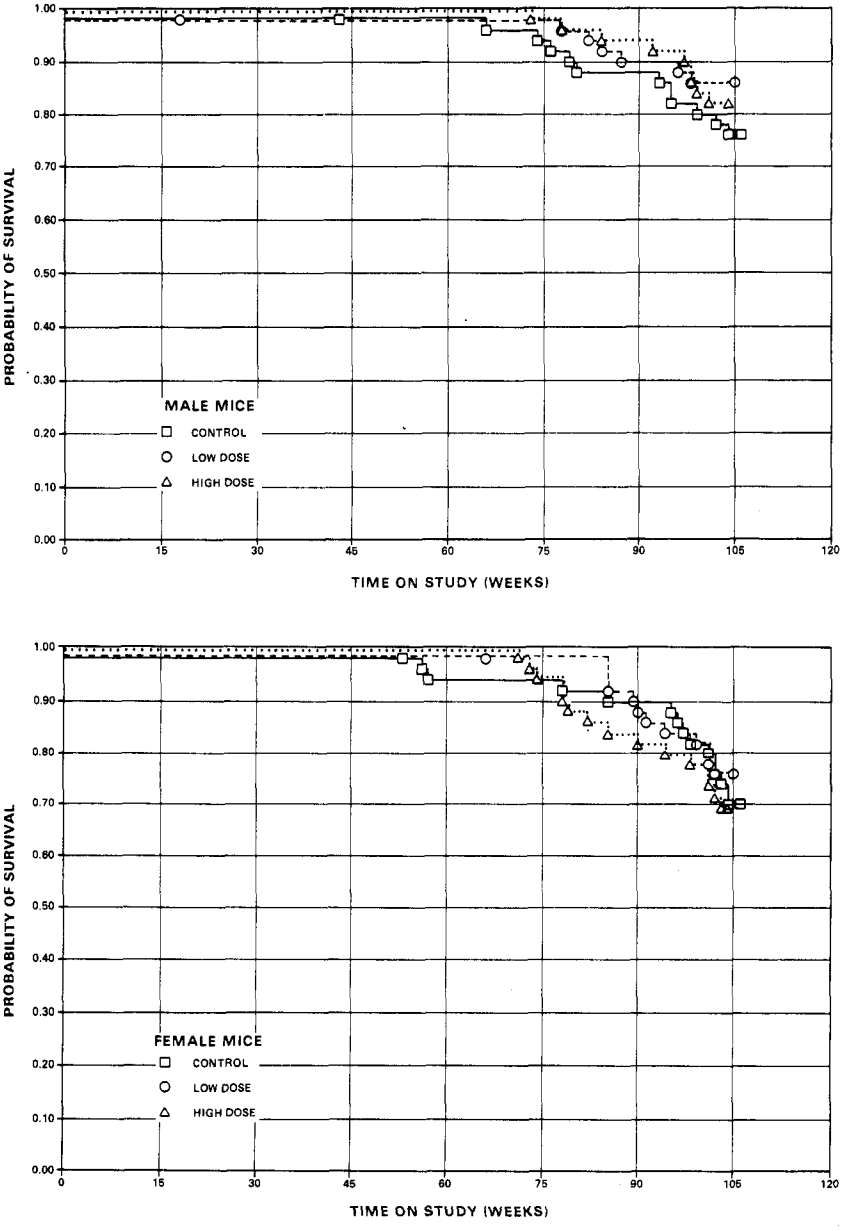


Figure 4. Survival Curves for Mice Fed Diets Containing D-Mannitol

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 for each individual animal in the male and female mouse studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Tables 10 and 11 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: Lymphocytic leukemia occurred in female mice in a statistically significant ($P<0.05$) positive trend (0/48, 2/48, 4/49), but lymphocytic lymphoma was observed in females in a statistically significant ($P<0.01$) negative trend (9/48, 3/48, 1/49). The combined incidences of lymphoma and leukemia did not differ significantly between dosed and control female mice (14/48, 13/48, 7/49). Tests of the incidence of hematopoietic tumors in male mice were not statistically significant.

Subcutaneous Tissues: Sarcomas occurred in male mice in a statistically significant ($P<0.05$) negative trend, but tests between the dosed and the control groups were not statistically significant (4/50, 1/50, 0/49).

Mammary Gland: Malignant tumors in female mice occurred in a statistically significant ($P<0.05$) negative trend, but no tests between the dosed groups and the controls were statistically significant (3/48, 0/48, 0/49).

Kidney: Nephrosis was observed in increased incidences in dosed mice of each sex: control males, 15/50 (30%); low-dose males, 29/50 (58%); high-dose males, 30/47 (64%); control females, 1/48 (2%); low-dose females, 3/48 (6%); high-dose females, 14/49 (29%). The lesion was mild in most mice and was characterized primarily by focal vacuolization of the renal tubular epithelium.

TABLE 10. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)*

	Control	Low Dose	High Dose
Subcutaneous Tissue: Fibrosarcoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	0/50 (0%)	0/49 (0%)
Adjusted *(c)*	6.8%	0.0%	0.0%
Terminal *(d)*	0/39 (0%)	0/43 (0%)	0/41 (0%)
Statistical Tests *(e)*			
Life Table	P=0.035N	P=0.115N	P=0.116N
Incidental Tumor Test	P=0.052N	P=0.189N	P=0.141N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.038N	P=0.121N	P=0.125N
Subcutaneous Tissue: All Sarcomas			
Tumor Rates			
Overall *(b)*	4/50 (8%)	1/50 (2%)	0/49 (0%)
Adjusted *(c)*	8.9%	2.3%	0.0%
Terminal *(d)*	0/39 (0%)	1/43 (2%)	0/41 (0%)
Statistical Tests *(e)*			
Life Table	P=0.024N	P=0.167N	P=0.062N
Incidental Tumor Test	P=0.028N	P=0.207N	P=0.056N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.027N	P=0.181N	P=0.061N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	6/50 (12%)	7/50 (14%)	7/49 (14%)
Adjusted *(c)*	15.4%	16.3%	16.1%
Terminal *(d)*	6/39 (15%)	7/43 (16%)	5/41 (12%)
Statistical Tests *(e)*			
Life Table	P=0.483	P=0.576	P=0.543
Incidental Tumor Test	P=0.454	P=0.576	P=0.506
Cochran-Armitage Trend, Fisher Exact Tests	P=0.426	P=0.500	P=0.484
Lung: Alveolar/Bronchiolar Carcinoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	6/50 (12%)	4/49 (8%)
Adjusted *(c)*	7.1%	13.5%	9.8%
Terminal *(d)*	2/39 (5%)	5/43 (12%)	4/41 (10%)
Statistical Tests *(e)*			
Life Table	P=0.459	P=0.292	P=0.525
Incidental Tumor Test	P=0.431	P=0.247	P=0.492
Cochran-Armitage Trend, Fisher Exact Tests	P=0.418	P=0.243	P=0.489
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	9/50 (18%)	12/50 (24%)	11/49 (22%)
Adjusted *(c)*	22.2%	27.1%	25.4%
Terminal *(d)*	8/39 (21%)	11/43 (26%)	9/41 (22%)
Statistical Tests *(e)*			
Life Table	P=0.409	P=0.403	P=0.455
Incidental Tumor Test	P=0.368	P=0.367	P=0.402
Cochran-Armitage Trend, Fisher Exact Tests	P=0.338	P=0.312	P=0.382

TABLE 10. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(b)*	3/50 (6%)	2/50 (4%)	2/49 (4%)
Adjusted *(c)*	7.5%	4.7%	4.7%
Terminal *(d)*	2/39 (5%)	2/43 (5%)	1/41 (2%)
Statistical Tests *(e)*			
Life Table	P=0.387N	P=0.458N	P=0.480N
Incidental Tumor Test	P=0.426N	P=0.543N	P=0.527N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.415N	P=0.500N	P=0.510N
Hematopoietic System: All Malignant Lymphoma			
Tumor Rates			
Overall *(b)*	7/50 (14%)	4/50 (8%)	5/49 (10%)
Adjusted *(c)*	16.8%	9.3%	10.8%
Terminal *(d)*	5/39 (13%)	4/43 (9%)	1/41 (2%)
Statistical Tests *(e)*			
Life Table	P=0.289N	P=0.217N	P=0.352N
Incidental Tumor Test	P=0.368N	P=0.313N	P=0.449N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.326N	P=0.262N	P=0.394N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	8/50 (16%)	4/50 (8%)	5/49 (10%)
Adjusted *(c)*	18.7%	9.3%	10.9%
Terminal *(d)*	5/39 (13%)	4/43 (9%)	1/41 (2%)
Statistical Tests *(e)*			
Life Table	P=0.198N	P=0.147N	P=0.257N
Incidental Tumor Test	P=0.268N	P=0.257N	P=0.343N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.226N	P=0.178N	P=0.290N
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	4/50 (8%)	1/49 (2%)
Adjusted *(c)*	2.6%	8.6%	2.4%
Terminal *(d)*	1/39 (3%)	2/43 (5%)	1/41 (2%)
Statistical Tests *(e)*			
Life Table	P=0.579N	P=0.209	P=0.751N
Incidental Tumor Test	P=0.580	P=0.159	P=0.751N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.593	P=0.181	P=0.747
Liver: Adenoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	6/50 (12%)	4/49 (8%)
Adjusted *(c)*	7.7%	13.4%	9.5%
Terminal *(d)*	3/39 (8%)	5/43 (12%)	3/41 (7%)
Statistical Tests *(e)*			
Life Table	P=0.459	P=0.292	P=0.527
Incidental Tumor Test	P=0.420	P=0.228	P=0.506
Cochran-Armitage Trend, Fisher Exact Tests	P=0.418	P=0.243	P=0.489

TABLE 10. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Liver: Carcinoma			
Tumor Rates			
Overall *(b)*	11/50 (22%)	8/50 (16%)	7/49 (14%)
Adjusted *(c)*	26.7%	17.8%	16.4%
Terminal *(d)*	9/39 (23%)	6/43 (14%)	6/41 (15%)
Statistical Tests *(e)*			
Life Table	P=0.151N	P=0.240N	P=0.189N
Incidental Tumor Test	P=0.192N	P=0.393N	P=0.223N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.190N	P=0.306N	P=0.232N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	14/50 (28%)	14/50 (28%)	11/49 (22%)
Adjusted *(c)*	34.0%	30.3%	25.3%
Terminal *(d)*	12/39 (31%)	11/43 (26%)	9/41 (22%)
Statistical Tests *(e)*			
Life Table	P=0.240N	P=0.476N	P=0.277N
Incidental Tumor Test	P=0.305N	P=0.492	P=0.323N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.305N	P=0.588	P=0.343N

(a) Dosed groups received doses of 25,000 or 50,000 ppm of D-mannitol 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 nonfatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

TABLE 11. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)*

	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/48 (6%)	2/48 (4%)	1/49 (2%)
Adjusted *(c)*	8.1%	5.3%	2.9%
Terminal *(d)*	3/37 (8%)	2/38 (5%)	0/34 (0%)
Statistical Tests *(e)*			
Life Table	P=0.246N	P=0.488N	P=0.337N
Incidental Tumor Test	P=0.261N	P=0.488N	P=0.355N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.217N	P=0.500N	P=0.301N
Hematopoietic System: Lymphocytic Leukemia			
Tumor Rates			
Overall *(b)*	0/48 (0%)	2/48 (4%)	4/49 (8%)
Adjusted *(c)*	0.0%	4.7%	8.5%
Terminal *(d)*	0/37 (0%)	0/38 (0%)	0/34 (0%)
Statistical Tests *(e)*			
Life Table	P=0.035	P=0.235	P=0.063
Incidental Tumor Test	P=0.085	P=0.134	P=0.175
Cochran-Armitage Trend, Fisher Exact Tests	P=0.039	P=0.247	P=0.061
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(b)*	9/48 (19%)	3/48 (6%)	1/49 (2%)
Adjusted *(c)*	22.8%	7.7%	2.9%
Terminal *(d)*	7/37 (19%)	2/38 (5%)	1/34 (3%)
Statistical Tests *(e)*			
Life Table	P=0.006N	P=0.063N	P=0.015N
Incidental Tumor Test	P=0.007N	P=0.085N	P=0.017N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.004N	P=0.060N	P=0.007N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(b)*	2/48 (4%)	5/48 (10%)	1/49 (2%)
Adjusted *(c)*	5.0%	11.7%	2.5%
Terminal *(d)*	1/37 (3%)	2/38 (5%)	0/34 (0%)
Statistical Tests *(e)*			
Life Table	P=0.455N	P=0.227	P=0.532N
Incidental Tumor Test	P=0.360N	P=0.303	P=0.577N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.403N	P=0.218	P=0.492N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(b)*	3/48 (6%)	2/48 (4%)	1/49 (2%)
Adjusted *(c)*	7.8%	5.3%	2.9%
Terminal *(d)*	2/37 (5%)	2/38 (5%)	1/34 (3%)
Statistical Tests *(e)*			
Life Table	P=0.248N	P=0.493N	P=0.339N
Incidental Tumor Test	P=0.261N	P=0.532N	P=0.355N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.217N	P=0.500N	P=0.301N

TABLE 11. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Hematopoietic System: Lymphoma, All Malignant			
Tumor Rates			
Overall *(b)*	14/48 (29%)	11/48 (23%)	3/49 (6%)
Adjusted *(c)*	33.9%	25.2%	8.2%
Terminal *(d)*	10/37 (27%)	6/38 (16%)	2/34 (6%)
Statistical Tests *(e)*			
Life Table	P=0.009N	P=0.321N	P=0.009N
Incidental Tumor Test	P=0.003N	P=0.262N	P=0.008N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.003N	P=0.321N	P=0.003N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	14/48 (29%)	13/48 (27%)	7/49 (14%)
Adjusted *(c)*	33.9%	28.7%	16.0%
Terminal *(d)*	10/37 (27%)	6/38 (16%)	2/34 (6%)
Statistical Tests *(e)*			
Life Table	P=0.108N	P=0.489N	P=0.117N
Incidental Tumor Test	P=0.035N	P=0.484N	P=0.054N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.054N	P=0.500N	P=0.062N
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	0/48 (0%)	2/48 (4%)	3/49 (6%)
Adjusted *(c)*	0.0%	5.3%	8.2%
Terminal *(d)*	0/37 (0%)	2/38 (5%)	2/34 (6%)
Statistical Tests *(e)*			
Life Table	P=0.069	P=0.244	P=0.108
Incidental Tumor Test	P=0.093	P=0.244	P=0.179
Cochran-Armitage Trend, Fisher Exact Tests	P=0.086	P=0.247	P=0.125
Liver: Carcinoma			
Tumor Rates			
Overall *(b)*	3/48 (6%)	2/48 (4%)	1/49 (2%)
Adjusted *(c)*	8.1%	5.3%	2.9%
Terminal *(d)*	3/37 (8%)	2/38 (5%)	1/34 (3%)
Statistical Tests *(e)*			
Life Table	P=0.244N	P=0.488N	P=0.335N
Incidental Tumor Test	P=0.244N	P=0.488N	P=0.335N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.217N	P=0.500N	P=0.301N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall (b)	3/48 (6%)	3/48 (6%)	2/49 (4%)
Adjusted (c)	8.1%	7.9%	5.9%
Terminal (d)	3/37 (8%)	3/38 (8%)	2/34 (6%)
Statistical Tests *(e)*			
Life Table	P=0.450N	P=0.652N	P=0.539N
Incidental Tumor Test	P=0.450N	P=0.652N	P=0.539N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.403N	P=0.661	P=0.490N

TABLE 11. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Mammary Gland: Mixed Tumor, Malignant			
Tumor Rates			
Overall *(b)*	3/48 (6%)	0/48 (0%)	0/49 (0%)
Adjusted *(c)*	7.9%	0.0%	0.0%
Terminal *(d)*	2/37 (5%)	0/38 (0%)	0/34 (0%)
Statistical Tests *(e)*			
Life Table	P=0.041N	P=0.120N	P=0.138N
Incidental Tumor Test	P=0.049N	P=0.147N	P=0.151N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.036N	P=0.121N	P=0.117N

(a) Dosed groups received doses of 25,000 or 50,000 ppm of D-mannitol 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 nonfatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

IV. DISCUSSION AND CONCLUSIONS

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The following prechronic studies of D-mannitol were conducted with F344/N rats and B6C3F1/N mice: a single-dose gavage study (300-5,000 mg/kg); a 14-day study (6,000-100,000 ppm in feed); and a 13-week study (3,000-50,000 ppm in feed). A carcinogenesis bioassay was then conducted by feeding diets containing 0, 25,000, or 50,000 ppm D-mannitol to rats and mice for 103 weeks.

All rats administered D-mannitol in the prechronic studies survived to the end of the test periods. The mean body weight gain for males administered 50,000 ppm in feed for 13 weeks was depressed 9.6% relative to that of the controls.

In the chronic study, survival and mean body weights were comparable for male rats fed diets containing 0, 25,000, or 50,000 ppm D-mannitol. Survival of female rats receiving 50,000 ppm was significantly greater ($P<0.05$) than that for females receiving 25,000 ppm, and somewhat greater than that for control females at the end of the study. Throughout the study, mean body weights of dosed female rats were slightly lower than the mean body weight of the control group. Feed consumption by control and dosed rats of each sex was similar.

All mice administered D-mannitol in the prechronic studies survived to the end of the test periods. Weight gains and feed consumption of mice fed diets containing 0-50,000 ppm D-mannitol for 13 weeks were similar. In the 2-year chronic study, survival, mean body weight gains, and feed consumption were similar for mice fed diets containing 0, 25,000, or 50,000 ppm D-mannitol.

Although both rats and mice may have been able to tolerate higher doses, 50,000 ppm was selected as the high dose because it is the maximum concentration of a test substance in feed recommended in the guidelines of the Bioassay Program (NCI, 1976).

No statistically significant incidences of neoplastic lesions were observed at any site in rats of either sex.

Dilatation of the gastric fundal gland was observed in increased incidence in female rats fed diets containing 25,000 or 50,000 ppm D-mannitol (control, 6/50, 12%; low-dose, 23/50, 46%; high-dose, 23/50, 46%).

Retinopathy and cataract formation occurred at increased incidences in male rats administered 50,000 ppm and in female rats administered 25,000 or 50,000 ppm in the chronic study. The incidences of these lesions in rats in this study are probably associated with the distance of the animals from the fluorescent light source. This observation seems consistent with the findings that age-related retinal degeneration in Fischer rats appeared to be exaggerated by light (Lai et al., 1978). In another study, Sprague-Dawley rats exposed continuously to light showed morphological damage to the retina (Reuter and Hobbelen, 1977). Further, different light sources, calibrated to deliver the same irradiances, have been shown to influence the latent period for tumor development and to induce reproductive changes (Chignell et al., in press, 1982). Cataract formation has also been associated with the marked elevation of the plasma concentration of monosaccharides structurally related to D-mannitol (White et al., 1978), but the relationship between cataracts and administration of D-mannitol in this study cannot be established from the data.

In female mice in the chronic study, lymphocytic leukemia occurred with a statistically significant positive trend ($P<0.05$), whereas lymphocytic lymphoma occurred with a statistically significant negative trend ($P<0.01$). The incidence of dosed female mice with lymphomas or leukemia was not statistically different from controls. The historical incidence in the Bioassay Program of control female B6C3F1/N mice with lymphocytic leukemia is 27/2819 (1%), the highest group incidence being 5/50. The historical incidence of control female mice with either lymphomas or leukemia is 729/2819 (25.9%), with a range of 8.0%-62.0% (Appendix J, Table J1).

Sarcomas in the subcutaneous tissue of male mice and malignant tumors of the mammary gland of female mice in the chronic study occurred with statistically significant ($P<0.05$) negative trends, but none of the tests between dosed groups and controls were statistically significant.

Mild nephrosis, characterized by focal vacuolization of the renal tubular epithelium, was observed in increased incidence in dosed male and female mice in the chronic study; this finding was considered to be related to administration of D-mannitol. Dilatation of the renal tubules, with vacuole formation, has been seen in post mortem examinations of humans administered D-mannitol (Schreiner and Maher, 1965). Male Sprague-Dawley rats intravenously infused with D-mannitol had increased vacuolization of the renal proximal convoluted tubules (Maunsbach et al.,

1962). This vacuolization was probably caused by osmotic imbalance.

The negative results from the available genotoxicity data on D-mannitol are compatible with the lack of any carcinogenic response from the long-term exposure study. The earliest reference located on the mutagenicity testing of D-mannitol is an FDA-supported study reported in 1974 (FDA, 1974; Green, 1977). Tests included the host-mediated assay in mice using *Salmonella typhimurium* G 46 and TA 1530 and *Saccharomyces cerevisiae* strain D 3, cytogenics in rat bone marrow and in WI-38 human cells, and a dominant lethal assay in rats. The NTP obtained reproducible (in three laboratories) negative results from *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 (NTP, 1981).

Conclusions: Under the conditions of this bioassay, D-mannitol was not carcinogenic for F344/N rats or B6C3F1 mice of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED DIETS CONTAINING D-MANNITOL

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED DIETS CONTAINING D-MANNITOL

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)	1 (2%)	
KERATOACANTHOMA		2 (4%)	
*SUBCUT TISSUE	(50)	(50)	(50)
BASAL-CELL TUMOR			1 (2%)
FIBROMA	2 (4%)	3 (6%)	5 (10%)
FIBROSARCOMA		1 (2%)	
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
RESPIRATORY SYSTEM			
*LARYNX	(50)	(50)	(50)
C-CELL CARCINOMA, INVASIVE		1 (2%)	
#LUNG/BRONCHUS	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
#LUNG	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
LEUKEMIA,NOS	1 (2%)		
UNDIFFERENTIATED LEUKEMIA	13 (26%)	14 (28%)	11 (22%)
#SPLEEN	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MANDIBULAR L. NODE	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
#THYMUS	(40)	(40)	(38)
THYMOMA	1 (3%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE		2 (4%)	1 (2%)
HEPATOCELLULAR CARCINOMA			1 (2%)
#PANCREAS	(50)	(50)	(50)
ACINAR-CELL ADENOMA		1 (2%)	
#SMALL INTESTINE	(50)	(49)	(50)
ADENOCARCINOMA, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(50)	(50)
ADENOMA, NOS	9 (20%)	10 (20%)	8 (16%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)	1 (2%)	1 (2%)
CORTICAL CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA	14 (28%)	10 (20%)	9 (18%)
#ADRENAL MEDULLA	(50)	(50)	(50)
GANGLIONEUROMA	1 (2%)		
#THYROID	(49)	(50)	(50)
FOLLICULAR-CELL ADENOMA	2 (4%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
C-CELL ADENOMA	8 (16%)	4 (8%)	5 (10%)
C-CELL CARCINOMA	2 (4%)	1 (2%)	1 (2%)
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET-CELL ADENOMA	3 (6%)	3 (6%)	4 (8%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA	1 (2%)		1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	
#PROSTATE	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		1 (2%)
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	45 (90%)	44 (88%)	45 (90%)
*SCROTUM	(50)	(50)	(50)
NEURILEMOMA, MALIGNANT			1 (2%)
NERVOUS SYSTEM			
#CEREBRAL CORTEX	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
SPECIAL SENSE ORGANS			
*EYE/CONJUNCTIVA	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	3 (6%)	2 (4%)	
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(50)	(50)
ADENOCARCINOMA, NOS, 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
*RIB	(50)	(50)	(50)
OSTEOSARCOMA			1 (2%)
BODY CAVITIES			
*THORAX	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
*MESENTERY	(50)	(50)	(50)
LIPOSARCOMA			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
FIBROSARCOMA		1 (2%)	
HEAD			
SQUAMOUS CELL CARCINOMA		1	
SQUAMOUS CELL CARCINOMA, INVASIV	1		
LEG			
SYNOVIAL SARCOMA	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	4	4
MORIBUND SACRIFICE	15	10	15
SCHEDULED SACRIFICE	6		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	23	36	31
ANIMAL MISSING			

@ 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	49	48
TOTAL PRIMARY TUMORS	114	109	101
TOTAL ANIMALS WITH BENIGN TUMORS	49	47	46
TOTAL BENIGN TUMORS	89	82	81
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	20	19
TOTAL MALIGNANT TUMORS	25	25	19
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	1
TOTAL SECONDARY TUMORS	1	3	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	1
TOTAL UNCERTAIN TUMORS		2	1
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 D-MANNITOL

	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)
FIBROMA	1 (2%)	1 (2%)	
RHABDOMYOSARCOMA	1 (2%)		
NEURILEMOMA, MALIGNANT		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA			2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		
NEURILEMOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA,NOS			1 (2%)
UNDIFFERENTIATED LEUKEMIA	10 (20%)	8 (16%)	4 (8%)
#BONE MARROW	(50)	(50)	(50)
NEURILEMOMA, METASTATIC		1 (2%)	
#MANDIBULAR L. NODE	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(50)	(50)
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
DIGESTIVE SYSTEM			
*LIP	(50)	(50)	(50)
BASAL-CELL CARCINOMA	1 (2%)		
*TONGUE	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
#PAROTID GLAND	(50)	(48)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE		1 (2%)	
#STOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
SQUAMOUS CELL CARCINOMA	1 (2%)		
#COLON	(50)	(50)	(49)
NEURILEMOMA, INVASIVE	1 (2%)		
URINARY SYSTEM			
#URINARY BLADDER	(48)	(49)	(48)
NEURILEMOMA, INVASIVE	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(47)	(48)
CARCINOMA,NOS	1 (2%)	2 (4%)	
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
ADENOMA, NOS	24 (48%)	15 (32%)	19 (40%)
#ADRENAL	(49)	(50)	(50)
CORTICAL ADENOMA	1 (2%)	4 (8%)	2 (4%)
PHEOCHROMOCYTOMA	2 (4%)	3 (6%)	1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	
#THYROID	(50)	(50)	(50)
FOLLICULAR-CELL ADENOMA	1 (2%)		1 (2%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	
C-CELL ADENOMA	6 (12%)	6 (12%)	3 (6%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#PALLIUM	(50)	(50)	(50)
ASTROCYTOMA	1 (2%)		
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	1 (2%)
ADENOSQUAMOUS CARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, INVASIV	1 (2%)		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
C-CELL CARCINOMA		2 (4%)	1 (2%)
#PANCREATIC ISLETS	(50)	(49)	(49)
ISLET-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	3 (6%)	3 (6%)	
FIBROMA		1 (2%)	
FIBROADENOMA	10 (20%)	14 (28%)	7 (14%)
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
ADENOSQUAMOUS CARCINOMA		2 (4%)	
#UTERUS	(50)	(50)	(50)
ENDOMETRIAL STROMAL POLYP	10 (20%)	5 (10%)	11 (22%)
ENDOMETRIAL STROMAL SARCOMA		2 (4%)	
NEURILEMOMA, MALIGNANT	1 (2%)		
#OVARY	(50)	(50)	(50)
GRANULOSA-CELL TUMOR	1 (2%)		
FIBROMA		1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*MESENTERY	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
HEAD			
SQUAMOUS CELL CARCINOMA, INVASIV		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	2	4	1
MORIBUND SACRIFICE	12	16	7
SCHEDULED SACRIFICE	6		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	30	30	42
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	45	44	36
TOTAL PRIMARY TUMORS	78	77	55
TOTAL ANIMALS WITH BENIGN TUMORS	37	35	32
TOTAL BENIGN TUMORS	56	51	48
TOTAL ANIMALS WITH MALIGNANT TUMORS	19	23	7
TOTAL MALIGNANT TUMORS	21	25	7
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	2	1
TOTAL SECONDARY TUMORS	4	5	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			

* 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 D-MANNITOL

CONTROL

ANIMAL NUMBER	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525
WEEKS ON STUDY	079	141	104	041	089	041	041	041	066	066	066	066	066	061	061	098	062	062	061	091	091	091	061	070	106
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	N	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA								X																	
SUBCUTANEOUS TISSUE	+	+	+	N	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
FIBROMA														X											
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	-	-	-	+	+	-	+	-	+	+	-	+	+	+	+	-	+	-	+	-	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
THYMOMA																									
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	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS				X																	X				X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																X									
PHEOCHROMOCYTOMA				X			X	X	X		X			X	X				X						
GANGLIONEUROMA								X																	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA							X																		
C-CELL ADENOMA									X				X				X								
C-CELL CARCINOMA																				X					
PARATHYROID	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									X
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
EYE APPENDAGES	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
SQUAMOUS CELL CARCINOMA																									
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					
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
OSTEOSARCOMA																								X	
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
LEUKEMIA,NOS																									
UNDIFFERENTIATED LEUKEMIA	X		X			X		X			X	X						X		X					
HEAD NOS																									
SQUAMOUS CELL CARCINOMA, INVASIVE																									
LEG NOS																									
SYNOVIAL SARCOMA																									

+: 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) CONTROL

ANIMAL NUMBER	52606	52707	52808	52909	53001	53101	53202	53303	53404	53505	53606	53707	53808	53909	54001	54101	54202	54303	54404	54505	54606	54707	54808	54909	55010	TOTAL TISSUES TUMORS
WEEKS ON STUDY	10 6	08 9	09 7	10 6	10 6	08 9	09 4	10 0	04 3	10 6	01 6	01 6	09 9	10 6	01 6	01 4	08 9	10 6	09 8	08 5	09 8	10 0	10 6	01 2	10 4	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA																								X		2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	-	36
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MALIG.LYMPHOMA, HISTIOCYTIC TYPE					X																					1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	-	+	-	-	+	+	-	-	+	+	40
THYMOMA	X																									1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	46
ADENOMA, NOS			X			X										X	X						X	X		9
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA	X	X											X				X				X			X		14
GANGLIONEUROMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																				X						2
C-CELL ADENOMA	X		X										X	X					X							8
C-CELL CARCINOMA																								X		2
PARATHYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	42
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA				X			X																			3
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	N	+	+	+	+	N	N	+	+	+	+	+	+	+	N	N	+	50*
FIBROADENOMA																										1
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	45
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS										X																1
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	50*
ADENOCARCINOMA, NOS																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
EYE APPENDAGES	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			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	50*
SQUAMOUS CELL CARCINOMA							X					X														3
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	50*
OSTEOSARCOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE									X																	1
LEUKEMIA,NOS	X																									1
UNDIFFERENTIATED LEUKEMIA		X		X									X						X		X					13
HEAD NOS																										
SQUAMOUS CELL CARCINOMA, INVASIVE			X																							1
LEG NOS																										
SYNOVIAL SARCOMA																				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 A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF D-MANNITOL

LOW DOSE

ANIMAL NUMBER	50 01	50 02	50 03	50 04	50 05	50 06	50 07	50 08	50 09	51 10	51 11	51 12	51 13	51 14	51 15	51 16	51 17	51 18	51 19	52 20	52 21	52 22	52 23	52 24	52 25
WEEKS ON STUDY	105	084	095	098	095	095	095	095	092	082	095	095	095	068	095	095	095	095	097	095	095	091	095	095	095
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
FIBROMA																									X
FIBROSARCOMA																									
FIBROUS HISTIOCYTOMA, MALIGNANT																	X								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT										X															
ALVEOLAR/BRONCHIOLAR ADENOMA							X																		
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	-	+	+	+	-	+	+	+	+	+	+	-	+	-	+	+	-	+	-	-	+	-	-	-
LARYNX	N	+	N	N	N	+	N	+	N	N	+	N	+	N	+	N	N	+	N	+	+	N	+	+	+
C-CELL CARCINOMA, INVASIVE								X																	
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT										X															
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA																									
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA						X																			
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS				X										X		X	X	X							
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA			X																						
CORTICAL CARCINOMA	X																								
PHEOCHROMOCYTOMA	X											X	X					X		X			X		X
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA													X												
C-CELL CARCINOMA								X																	
PARATHYROID	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA											X						X								X
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
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
ADENOMA, NOS				X																					
ADENOCARCINOMA, NOS					X																				
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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															
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																									
UNDIFFERENTIATED LEUKEMIA	X				X	X							X				X		X						
HEAD NOS																									
SQUAMOUS CELL CARCINOMA		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	52606	52707	52808	52909	53011	53112	53312	53413	53513	53613	53706	53805	53905	54001	54111	54212	54313	54414	54515	54616	54717	54818	54919	55010	TOTAL
WEEKS ON STUDY	105	092	051	080	095	015	055	055	0515	0515	0806	0505	0515	0904	0105	0105	0105	0105	0105	0105	0818	0818	0105	0105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA													X												1
KERATOACANTHOMA													X								X				2
SUBCUTANEOUS TISSUE	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	50*
FIBROMA																				X					3
FIBROSARCOMA																					X				1
FIBROUS HISTIOCYTOMA, MALIGNANT																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																									1
ALVEOLAR/BRONCHIOLAR ADENOMA							X																		1
ALVEOLAR/BRONCHIOLAR CARCINOMA			X																						2
TRACHEA	-	-	-	+	-	+	+	-	+	+	+	-	+	+	+	-	-	-	+	+	+	+	+	+	31
LARYNX	+	+	+	N	+	N	N	+	N	N	N	+	N	N	N	+	+	+	N	N	N	N	N	N	50*
C-CELL CARCINOMA, INVASIVE																									1
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																									1
THYMUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ACINAR-CELL ADENOMA																				X					1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA																									1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS	X			X			X	X														X			10
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																									1
CORTICAL CARCINOMA																									1
PHEOCHROMOCYTOMA	X												X			X									10
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA									X						X							X			4
C-CELL CARCINOMA																									1
PARATHYROID	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																									3
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	50*
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	44
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	50*
ADENOMA, NOS																									1
ADENOCARCINOMA, NOS																									1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	50*
SQUAMOUS CELL CARCINOMA												X													2
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*
FIBROSARCOMA		X																							1
UNDIFFERENTIATED LEUKEMIA			X	X							X	X	X		X								X	X	14
HEAD NOS																									
SQUAMOUS CELL CARCINOMA																									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 A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF D-MANNITOL

HIGH DOSE

ANIMAL NUMBER	50101	50201	50301	50401	50501	50601	50701	50801	50901	51001	51101	51201	51301	51401	51501	51601	51701	51801	51901	52001	52101	52201	52301	52401	52501
WEEKS ON STUDY	104	105	104	104	104	104	104	104	104	104	092	087	066	096	104	104	104	104	104	131	096	104	104	104	104
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL TUMOR																									
FIBROMA	X							X		X	X														
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS		X																							
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	-	+	+	-	+	+	+	-	-	+	+	+	-	+	+	+	+	-	+	+	+	-	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	-	-	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS													X												
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS				X			X								X	X				X					
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA			X	X			X				X						X				X				
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA							X															X			X
C-CELL CARCINOMA																									
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	-	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA								X																	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	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
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS, METASTATIC		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
ADENOCARCINOMA, NOS, METASTATIC		X																							
OSTEOSARCOMA																									
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
LIPOSARCOMA																									
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				
SCROTUM NOS																									
NEURILEMOMA, MALIGNANT																									

+: 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) HIGH DOSE

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM	
SUBCUTANEOUS TISSUE	50*
BASAL-CELL TUMOR	1
FIBROMA	5
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	50
ADENOCARCINOMA, NOS	1
ALVEOLAR/BRONCHIOLAR ADENOMA	1
ALVEOLAR/BRONCHIOLAR CARCINOMA	1
TRACHEA	30
HEMATOPOIETIC SYSTEM	
BONE MARROW	50
SPLEEN	50
LYMPH NODES	50
THYMUS	38
CIRCULATORY SYSTEM	
HEART	50
DIGESTIVE SYSTEM	
SALIVARY GLAND	49
LIVER	50
NEOPLASTIC NODULE	1
HEPATOCELLULAR CARCINOMA	1
BILE DUCT	50
GALLBLADDER & COMMON BILE DUCT	50*
PANCREAS	50
ESOPHAGUS	50
STOMACH	50
SMALL INTESTINE	50
ADENOCARCINOMA, NOS	1
LARGE INTESTINE	49
URINARY SYSTEM	
KIDNEY	50
URINARY BLADDER	49
ENDOCRINE SYSTEM	
PITUITARY	50
ADENOMA, NOS	8
ADRENAL	50
CORTICAL ADENOMA	1
PHEOCHROMOCYTOMA	9
THYROID	50
C-CELL ADENOMA	5
C-CELL CARCINOMA	1
PARATHYROID	45
PANCREATIC ISLETS	50
ISLET-CELL ADENOMA	4
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50*
FIBROADENOMA	1
TESTIS	50
INTERSTITIAL-CELL TUMOR	45
PROSTATE	50
ADENOMA, NOS	1
NERVOUS SYSTEM	
BRAIN	50
ADENOCARCINOMA, NOS, METASTATIC	1
MUSCULOSKELETAL SYSTEM	
BONE	50*
ADENOCARCINOMA, NOS, METASTATIC	1
OSTEOSARCOMA	1
BODY CAVITIES	
MESENTERY	50*
LIPOSARCOMA	1
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50*
UNDIFFERENTIATED LEUKEMIA	11
SCROTUM NOS	
NEURILEMOMA, MALIGNANT	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 A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF D-MANNITOL

CONTROL

ANIMAL NUMBER	50111	50203	50304	50404	50505	50607	50714	50808	50900	51041	51106	51116	51206	51306	51416	51563	51617	51789	51896	51910	52006	52116	52216	52316	52406	52516
WEEKS ON STUDY	104	104	104	100	095	097	104	100	104	106	106	106	106	106	106	063	089	089	096	106	106	106	106	106	100	106
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE FIBROMA	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RHABDOMYOSARCOMA																X										
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI ADENOCARCINOMA, NOS, METASTATIC ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
							X																			
TRACHEA	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+	−	+	+
CIRCULATORY SYSTEM																										
HEART ADENOCARCINOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
ORAL CAVITY BASAL-CELL CARCINOMA	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
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	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH SQUAMOUS CELL CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE NEURILEMOMA, INVASIVE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER NEURILEMOMA, INVASIVE	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
PITUITARY CARCINOMA,NOS ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
			X	X		X			X		X					X	X	X	X	X	X		X	X		X
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+
											X															
THYROID FOLLICULAR-CELL ADENOMA C-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
												X											X		X	
PARATHYROID	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND ADENOCARCINOMA, NOS FIBROADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+
					X					X	X											X				X
PREPUTIAL/CLITORAL GLAND ADENOMA, 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
				X																						
UTERUS ENDOMETRIAL STROMAL POLYP NEURILEMOMA, MALIGNANT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	X							X	X	X		X														
OVARY GRANULOSA-CELL TUMOR	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
BRAIN ASTROCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																										
MEDIASTINUM ALVEOLAR/BRONCHIOLAR CA, INVASIVE	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
							X																			
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	N
				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 A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	52606	52707	52808	52909	53006	53101	53202	53303	53404	53505	53606	53707	53808	53909	54001	54101	54202	54303	54404	54505	54606	54707	54808	54909	55006	TOTAL
WEEKS ON STUDY	076	106	106	106	106	106	106	106	096	016	106	106	106	106	093	106	106	094	096	106	106	106	106	106	106	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA												X														1
RHABDOMYOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS, METASTATIC																		X								1
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	43
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	-	-	+	+	+	+	+	+	+	-	+	+	+	-	-	+	-	-	+	+	+	+	+	+	36
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																		X								1
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*
BASAL-CELL CARCINOMA																									X	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	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEURILEMOMA, INVASIVE	X																									1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NEURILEMOMA, INVASIVE	X																									1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																										1
ADENOMA, NOS					X	X	X			X			X		X	X	X	X	X	X						24
ADRENAL	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA																		X								2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																	X									1
C-CELL ADENOMA		X																		X		X				4
PARATHYROID	+	+	+	+	-	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	43
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS							X		X											X			X			3
FIBROADENOMA										X	X		X		X											10
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	50*
ADENOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP															X	X		X					X	X		10
NEURILEMOMA, MALIGNANT	X																									1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULOSA-CELL TUMOR																				X						1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA		X																								1
BODY CAVITIES																										
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ALVEOLAR/BRONCHIOLAR CA, INVASIVE																										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*
UNDIFFERENTIATED LEUKEMIA		X		X														X			X	X		X		10

* 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 D-MANNITOL

LOW DOSE

ANIMAL NUMBER	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525
WEEKS ON STUDY	105	105	105	105	105	105	096	105	105	102	105	091	105	099	089	105	105	105	069	092	105	105	104	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																						X			
NEURILEMOMA, MALIGNANT							X																		
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
NEURILEMOMA, METASTATIC							X																		
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEURILEMOMA, METASTATIC							X																		
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT															X										
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	N
SQUAMOUS CELL PAPILLOMA												X													
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE															X										
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
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA			X		X			X																	
PHEOCHROMOCYTOMA														X											
PHEOCHROMOCYTOMA, MALIGNANT														X											
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA				X	X		X			X			X												
C-CELL CARCINOMA											X														
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS		X											X												
FIBROMA													X												
FIBROADENOMA	X	X	X						X		X										X			X	
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
ADENOSQUAMOUS CARCINOMA									X																
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP		X				X			X			X						X							
ENDOMETRIAL STROMAL SARCOMA															X										
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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										
ADENOSQUAMOUS CARCINOMA																									
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
SARCOMA, NOS										X															
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	X	X	N	N	N	N	N
UNDIFFERENTIATED LEUKEMIA																									
HEAD NOS																									
SQUAMOUS CELL CARCINOMA, INVASIVE															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 A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	52616	52707	52808	52909	53011	53112	53313	53445	53587	53689	53715	53815	53909	54007	54105	54205	54308	54494	54516	54617	54818	54950	55070	TOTAL
WEEKS ON STUDY	105	105	082	095	097	105	103	105	087	089	105	105	090	078	095	105	082	094	105	105	105	095	070	TISSUES TUMORS
INTEGUMENTARY SYSTEM																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	50*
FIBROMA																								1
NEURILEMOMA, MALIGNANT																								1
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NEURILEMOMA, METASTATIC																								1
TRACHEA	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	-	+ 43
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEURILEMOMA, METASTATIC																								1
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																								1
THYMUS	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	36
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	50*
SQUAMOUS CELL PAPILLOMA																								1
SALIVARY GLAND	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SQUAMOUS CELL CARCINOMA, INVASIVE																								1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																								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	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																								
PITUITARY	-	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
CARCINOMA,NOS										X													X	2
ADENOMA, NOS				X		X					X		X					X	X	X				15
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA						X																		4
PHEOCHROMOCYTOMA																X					X			3
PHEOCHROMOCYTOMA, MALIGNANT																								1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA	X																							1
C-CELL ADENOMA												X												6
C-CELL CARCINOMA																						X		2
PARATHYROID	-	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	47
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS								X																3
FIBROMA																								1
FIBROADENOMA		X				X		X				X			X		X	X						14
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	50*
ADENOSQUAMOUS CARCINOMA			X																					2
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP																								5
ENDOMETRIAL STROMAL SARCOMA															X									2
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA																X								1
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	50*
SQUAMOUS CELL CARCINOMA																								1
ADENOSQUAMOUS CARCINOMA																X								1
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	50*
SARCOMA, 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	50*
UNDIFFERENTIATED LEUKEMIA										X				X	X				X	X				8
HEAD NOS																								
SQUAMOUS CELL CARCINOMA, INVASIVE																								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 A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF D-MANNITOL

HIGH DOSE

ANIMAL NUMBER	50101	50102	50103	50104	50105	50106	50107	50108	50109	51110	51111	51112	51113	51114	51115	51116	51117	51118	51119	52120	52121	52122	52123	52124	52125
WEEKS ON STUDY	104	104	081	081	083	094	101	104	104	094	101	104	094	094	081	096	094	094	094	076	104	104	104	091	104
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT						X																			
ADENOMA, NOS				X	X				X								X			X	X		X	X	X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																	X								
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
C-CELL ADENOMA																	X								
C-CELL CARCINOMA																							X		
PARATHYROID	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA	X								X												X				
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP			X					X						X									X		X
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
SQUAMOUS CELL CARCINOMA						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
LEUKEMIA,NOS																									
UNDIFFERENTIATED 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 A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	52606	52707	52808	52909	53010	53111	53212	53313	53414	53515	53616	53717	53818	53919	54020	54121	54222	54323	54424	54525	54626	54727	54828	54929	55030	TOTAL
WEEKS ON STUDY	104	104	104	104	104	971	905	105	105	105	105	105	105	105	105	105	105	889	105	105	105	105	105	913	105	TISSUES / TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA										X		X														2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	-	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	-	-	+	41
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	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA			X																							1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
SQUAMOUS CELL CARCINOMA, METASTAT																										1
ADENOMA, NOS		X			X	X	X		X			X					X			X	X		X		19
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA								X																		2
PHEOCHROMOCYTOMA		X																								1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																	X									1
C-CELL ADENOMA		X													X											3
C-CELL CARCINOMA																										1
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	47
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA			X																							1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROADENOMA	X	X											X	X												7
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP			X						X		X		X	X		X										11
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	50*
SQUAMOUS CELL CARCINOMA																										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*
LEUKEMIA,NOS		X																								1
UNDIFFERENTIATED LEUKEMIA									X									X								4

* 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 D-MANNITOL

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED DIETS CONTAINING D-MANNITOL

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
NEURILEMOMA, MALIGNANT			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(49)
SARCOMA, NOS	1 (2%)		
FIBROMA	2 (4%)		
FIBROSARCOMA	3 (6%)		
RHABDOMYOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
UNDIFFERENTIATED CARCINOMA	1 (2%)		
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)		5 (10%)
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (12%)	7 (14%)	7 (14%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	6 (12%)	4 (8%)
TUBULAR-CELL ADENOCARCINOMA, MET		1 (2%)	
PHEOCHROMOCYTOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
MALIGNANT LYMPHOMA, NOS			2 (4%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	1 (2%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	1 (2%)	
UNDIFFERENTIATED LEUKEMIA	1 (2%)		
#SPLEEN	(49)	(49)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MESENTERIC L. NODE	(49)	(50)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
#LIVER	(50)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#DUODENUM	(45)	(47)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)
#SPLEEN	(49)	(49)	(47)
HEMANGIOSARCOMA	1 (2%)	1 (2%)	
#LIVER	(50)	(50)	(49)
HEMANGIOSARCOMA		3 (6%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
HEPATOCELLULAR ADENOMA	3 (6%)	6 (12%)	4 (8%)
HEPATOCELLULAR CARCINOMA	11 (22%)	8 (16%)	7 (14%)
MIXED HEPATO/CHOLANGIO CARCINOMA		1 (2%)	
#PYLORUS	(49)	(49)	(48)
ADENOMATOUS POLYP, NOS			1 (2%)
#CECUM	(43)	(48)	(47)
LEIOMYOSARCOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(47)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	
#U. BLADDER/MUCOSA	(48)	(50)	(46)
LEIOMYOMA		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#ADRENAL	(49)	(50)	(46)
PHEOCHROMOCYTOMA, MALIGNANT			1 (2%)
#THYROID	(50)	(50)	(47)
C-CELL CARCINOMA			1 (2%)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
ADENOCARCINOMA, NOS			1 (2%)
*EPIDIDYMIS	(50)	(50)	(49)
CARCINOMA,NOS	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(49)
ADENOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(49)
MIXED HEPATO/CHOLANGIOCA, METAST		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SARCOMA, NOS			1 (2%)
LEG			
NEUROFIBROSARCOMA	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	5	4
MORIBUND SACRIFICE	6	2	5
SCHEDULED SACRIFICE	5		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	33	43	41
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	33	26	26
TOTAL PRIMARY TUMORS	42	41	34
TOTAL ANIMALS WITH BENIGN TUMORS	10	13	10
TOTAL BENIGN TUMORS	12	15	12
TOTAL ANIMALS WITH MALIGNANT TUMORS	27	18	20
TOTAL MALIGNANT TUMORS	30	26	22
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	2	6
TOTAL SECONDARY TUMORS	2	2	6
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 D-MANNITOL

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	48	49
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(48)	(49)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
SQUAMOUS CELL CARCINOMA	1 (2%)		
BASAL-CELL CARCINOMA	1 (2%)		
*SUBCUT TISSUE	(48)	(48)	(49)
RHABDOMYOSARCOMA		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(48)	(48)	(49)
CARCINOMA, NOS, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM			
#BRAIN	(48)	(48)	(49)
MALIGNANT RETICULOSIS			1 (2%)
*SPINAL CORD	(48)	(48)	(49)
MALIGNANT RETICULOSIS			1 (2%)
*CAUDA EQUINA	(48)	(48)	(49)
MALIGNANT RETICULOSIS			1 (2%)
*MULTIPLE ORGANS	(48)	(48)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	8 (17%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	4 (8%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)	2 (4%)	1 (2%)
LYMPHOCYTIC LEUKEMIA		2 (4%)	4 (8%)
#SPLEEN	(48)	(47)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
#MANDIBULAR L. NODE	(48)	(47)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#ILIAC LYMPH NODE	(48)	(47)	(48)
LEIOMYOSARCOMA, INVASIVE	1 (2%)		
#AXILLARY LYMPH NODE	(48)	(47)	(48)
RHABDOMYOSARCOMA, METASTATIC		1 (2%)	
#LIVER	(48)	(48)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#PEYER'S PATCH	(47)	(42)	(44)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*SKIN	(48)	(48)	(49)
HEMANGIOMA		1 (2%)	1 (2%)
#BONE MARROW	(47)	(47)	(47)
HEMANGIOSARCOMA		1 (2%)	
#SPLEEN	(48)	(47)	(48)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(48)	(48)	(49)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
#UTERUS	(47)	(48)	(49)
HEMANGIOSARCOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(48)	(48)	(49)
HEPATOCELLULAR ADENOMA		1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA	3 (6%)	2 (4%)	1 (2%)
URINARY SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(44)	(47)
ADENOMA, NOS		2 (5%)	
#ADRENAL	(48)	(47)	(48)
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(46)	(48)	(49)
FOLLICULAR-CELL ADENOMA	1 (2%)		1 (2%)
FOLLICULAR-CELL CARCINOMA		2 (4%)	
#PANCREATIC ISLETS	(48)	(45)	(45)
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(48)	(48)	(49)
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	
INTRADUCTAL CARCINOMA	1 (2%)		
ADENOSQUAMOUS CARCINOMA	1 (2%)		
ADENOCA/SQUAMOUS METAPLASIA		1 (2%)	
MIXED TUMOR, MALIGNANT	3 (6%)		
#UTERUS	(47)	(48)	(49)
LEIOMYOSARCOMA	1 (2%)		
#OVARY	(44)	(44)	(46)
LUTEOMA		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(48)	(48)	(49)
EPENDYMOMA	1 (2%)		
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(48)	(48)	(49)
CARCINOMA,NOS			1 (2%)
ADENOMA, NOS			1 (2%)
CYSTADENOMA, NOS			1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*FEMUR	(48)	(48)	(49)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(48)	(48)	(49)
SARCOMA, NOS			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	5	9	12
MORIBUND SACRIFICE	10	3	3
SCHEDULED SACRIFICE	5		
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	30	38	34
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	26	24	18
TOTAL PRIMARY TUMORS	33	31	23
TOTAL ANIMALS WITH BENIGN TUMORS	3	4	6
TOTAL BENIGN TUMORS	3	6	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	21	14
TOTAL MALIGNANT TUMORS	29	25	16
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	1
TOTAL SECONDARY TUMORS	1	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
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 B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF D-MANNITOL

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	095	094	104	104	104	094	066	104	106	106	106	106	106	106	096	086	096	099	096	086	086	074	106	151	106
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROMA																									
FIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
UNDIFFERENTIATED CARCINOMA											X														
HEPATOCELLULAR CARCINOMA, METASTA	X												X	X					X						
ALVEOLAR/BRONCHIOLAR ADENOMA						X																			
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	-	+	+	+	-	+	-	-	-	-	+	-	-	+	+	-	+	-	+	-	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																							X		
LYMPH NODES	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																									
THYMUS	-	-	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA													X												
HEPATOCELLULAR CARCINOMA	X	X													X	X		X							X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE													X												
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																						X			
MALIGNANT LYMPHOMA, MIXED TYPE																									
UNDIFFERENTIATED LEUKEMIA																									
LEG NOS														X											
NEUROFIBROSARCOMA																									

+: 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	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL
WEEKS ON STUDY	106	106	106	106	106	076	095	102	106	106	106	106	106	080	093	079	106	106	105	106	106	043	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS														X												1
FIBROMA								X																X		2
FIBROSARCOMA							X	X								X										3
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
UNDIFFERENTIATED CARCINOMA																										1
HEPATOCELLULAR CARCINOMA, METASTA																										2
ALVEOLAR/BRONCHIOLAR ADENOMA		X	X																					X		6
ALVEOLAR/BRONCHIOLAR CARCINOMA						X																			X	3
TRACHEA	+	-	-	-	-	+	+	+	+	+	-	-	-	+	+	+	-	+	+	-	+	-	-	-	-	25
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA			X																							1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE								X																		1
MALIGNANT LYMPHOMA, MIXED TYPE																				X						1
THYMUS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	-	+	+	+	+	41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA			X		X																					3
HEPATOCELLULAR CARCINOMA											X							X		X			X		X	11
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	N	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	45
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	43
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	42
ADRENAL	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PARATHYROID	+	+	-	+	-	-	+	-	+	+	-	-	+	+	+	-	+	+	-	+	-	+	+	+	-	34
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA,NOS									X																	1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	50*
ADENOMA, 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	50*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE											X															2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
MALIGNANT LYMPHOMA, MIXED TYPE																			X							1
UNDIFFERENTIATED LEUKEMIA															X											1
LEG NOS																										
NEUROFIBROSARCOMA																										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 D-MANNITOL

LOW DOSE

ANIMAL NUMBER	00011	00012	00013	00014	00015	00016	00017	00018	00019	00020	00111	00112	00113	00114	00115	00116	00117	00118	00119	00120	00211	00212	00213	00214	00215
WEEKS ON STUDY	01108	01105	01105	00998	01005	01005	01105	01082	01005	01005	01105	01096	01005	01005	01084	01005	01005	01005	01005	01005	01105	01105	01105	01105	01105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
RHABDOMYOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA										X											X				X
ALVEOLAR/BRONCHIOLAR CARCINOMA					X			X														X			
TUBULAR-CELL ADENOCARCINOMA, META																							X		
TRACHEA	+	-	-	+	-	+	-	+	+	-	-	+	+	+	+	+	+	-	+	-	-	+	-	-	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	-	+	+	+	+	+	+	-	-	-	+	+	+	+	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA					X	X														X					
HEPATOCELLULAR CARCINOMA				X			X					X												X	
MIXED HEPATO/CHOLANGIO CARCINOMA								X																	
HEMANGIOSARCOMA																								X	
MALIG LYMPHOMA HISTIOCYTIC TYPE																								X	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIG LYMPHOMA, LYMPHOCYTIC TYPE																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA																					X				
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOCARCINOMA																				X					
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOMA																						X			
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+		+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY CYSTADENOMA, NOS																									
PARATHYROID	-		-	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+		+	+	-	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
MIXED HEPATO/CHOLANGIOCA, METASTA								X																	
MALIG LYMPHOMA LYMPHOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																									

+ 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	101	105	105	105	078	105	087	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	N	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
RHABDOMYOSARCOMA			X																							1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA					X								X							X						7
ALVEOLAR/BRONCHIOLAR CARCINOMA										X										X		X				6
TUBULAR-CELL ADENOCARCINOMA, META																										1
TRACHEA	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	17
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA								X																		1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	-	+	+	+	+	-	+	43
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA		X				X							X													6
HEPATOCELLULAR CARCINOMA			X		X					X				X												8
MIXED HEPATO/CHOLANGIO CARCINOMA																										1
HEMANGIOSARCOMA						X						X														3
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE										X																1
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LEIOMYOSARCOMA																										1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOCARCINOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LEIOMYOMA																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PAPILLARY CYSTADENOMA, NOS				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	50*
TESTIS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	50*
MIXED HEPATO/CHOLANGIOCA, METASTA																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		X																								1
MALIGNANT LYMPHOMA, MIXED TYPE					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 D-MANNITOL

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	104	104	104	104	104	104	104	104	073	104	104	104	078	104	104	104	098	104	098	104	104	104	104	099	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	A	+	+	+	+	N	+
NEURILEMOMA, MALIGNANT			X		C																				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA									X				X												
ALVEOLAR/BRONCHIOLAR ADENOMA	X										X						X	X					X		
ALVEOLAR/BRONCHIOLAR CARCINOMA							X																		
PHEOCHROMOCYTOMA, METASTATIC																									
TRACHEA	+	-	+	-	+	-	-	+	+	-	-	+	+	-	-	-	+	-	A	-	-	-	-	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE										X															
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	+
THYMUS	+	+	-	-	-	-	+	-	+	+	+	+	-	+	+	+	+	-	A	+	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA			X															X		X				X	
HEPATOCELLULAR CARCINOMA					X				X				X												
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	+	N	+	N	+	+	+	N	+	+	+	N	N	A	+	+	+	+	N	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	A	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	+
ADENOMATOUS POLYP, NOS																				X					
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	#	+	A	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	-
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
PHEOCHROMOCYTOMA, MALIGNANT																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	+
C-CELL CARCINOMA																									
PARATHYROID	+	+	+	-	+	-	+	+	-	-	+	-	-	+	+	-	-	-	A	-	-	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N
ADENOCARCINOMA, NOS																									
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N
SARCOMA, NOS																	X								
HEMANGIOSARCOMA																									
MALIGNANT LYMPHOMA, NOS													X												
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																								X	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									

+: 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) 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	104	104	101	104	104	104	104	104	104	097	104	084	104	104	104	104	104	104	104	104	104	092	104	104		
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	49*
NEURILEMOMA, MALIGNANT																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA									X						X						X					5
ALVEOLAR/BRONCHIOLAR ADENOMA	X									X																7
ALVEOLAR/BRONCHIOLAR CARCINOMA					X			X																X		4
PHEOCHROMOCYTOMA, METASTATIC										X																1
TRACHEA	-	+	+	+	-	-	-	-	+	+	+	+	-	-	-	-	-	-	-	-	+	-	+	-	-	18
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	46
SPLEEN	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
THYMUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA																										4
HEPATOCELLULAR CARCINOMA								X	X						X						X					7
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	N	N	+	+	+	+	+	+	N	N	+	+	+	+	N	+	+	+	+	N	+	+	+	+	49*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOMATOUS POLYP, NOS																										1
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	44
ADRENAL	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	46
PHEOCHROMOCYTOMA, MALIGNANT										X																1
THYROID	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-CELL CARCINOMA															X											1
PARATHYROID	+	+	-	+	+	-	-	+	+	+	+	+	-	+	-	+	-	-	-	-	-	+	+	+		27
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		49*
ADENOCARCINOMA, NOS																						X				1
TESTIS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	49*
SARCOMA, NOS																										1
HEMANGIOSARCOMA																	X									1
MALIGNANT LYMPHOMA, NOS			X																							2
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE												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 D-MANNITOL

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	104	104	104	104	104	102	106	106	098	106	106	106	106	106	053	103	106	106	106	106	106	106	106	106	106
INTEGUMENTARY SYSTEM																									
SKIN	+	+	N	+	+	+	+	+	+	+	N	+	+	+	A	+	+	+	+	+	+	+	N	+	+
SQUAMOUS CELL PAPILLOMA		X																							
SQUAMOUS CELL CARCINOMA																									
BASAL-CELL CARCINOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA					X					X	X														
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	-	-	-	-	-	+	-	+	+	+	-	-	-	+	A	+	+	-	+	+	-	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	-	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE											X														
MALIGNANT LYMPHOMA, MIXED TYPE																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA, INVASIVE																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																					X				
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	-	+	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	-
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA	X																							X	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	N	+	+	+	+	+	N	+	+	A	+	+	+	+	+	N	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	-	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	-	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	A	+	+	+	+	+	+	-	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	+	-	+	+	+	-	-	+	-	+	+	+	-	-	A	+	-	-	+	+	+	-	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	N	+	+	+	+	+	+	+	+	+	+	+	A	+	+	N	+	+	+	+	N	+	+
ADENOCARCINOMA, NOS																									
INTRADUCTAL CARCINOMA																									
ADENOSQUAMOUS CARCINOMA	X																								
MIXED TUMOR, MALIGNANT											X					X									
UTERUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA																									
OVARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
EPENDYMOMA			X																						
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				X		X								X				X							
MALIG.LYMPHOMA, HISTIOCYTIC TYPE									X																
MALIGNANT LYMPHOMA, MIXED TYPE																									

+: 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	0262	0278	0290	0311	0312	0334	0356	0376	0384	0396	0401	0411	0423	0441	0465	0467	0481	0496	0501	TOTAL
WEEKS ON STUDY	1006	1002	1061	0785	0577	1061	0997	0955	1056	0556	1064	1046	1066	1061	1066	0961	1011	1061	1066	TISSUES TUMORS
INTEGUMENTARY SYSTEM																				
SKIN	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48*
SQUAMOUS CELL PAPILLOMA														X						1
SQUAMOUS CELL CARCINOMA																				1
BASAL-CELL CARCINOMA																			X	1
RESPIRATORY SYSTEM																				
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
ALVEOLAR/BRONCHIOLAR ADENOMA																				1
ALVEOLAR/BRONCHIOLAR CARCINOMA																				2
TRACHEA	+	+	+	+	+	+	+	+	+	A	+	+	+	-	+	+	+	-	+	31
HEMATOPOIETIC SYSTEM																				
BONE MARROW	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE														X						1
MALIGNANT LYMPHOMA, MIXED TYPE																				1
LYMPH NODES	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
LEIOMYOSARCOMA, INVASIVE																	X			1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																				1
THYMUS	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	-	+	+	44
CIRCULATORY SYSTEM																				
HEART	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																				
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
HEPATOCELLULAR CARCINOMA			X																	3
BILE DUCT	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	+	A	N	N	+	+	+	+	N	+	+	48*
PANCREAS	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																				
KIDNEY	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
URINARY BLADDER	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																				
PITUITARY	+	+	+	+	+	+	+	+	+	A	+	+	-	+	+	-	+	+	+	45
ADRENAL	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
THYROID	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	46
FOLLICULAR-CELL ADENOMA																		X		1
PARATHYROID	-	-	+	+	-	+	+	+	-	+	A	+	+	+	-	+	-	-	+	29
REPRODUCTIVE SYSTEM																				
MAMMARY GLAND	+	+	+	+	+	+	+	N	+	+	A	+	+	+	+	+	+	+	+	48*
ADENOCARCINOMA, NOS						X														1
INTRADUCTAL CARCINOMA														X						1
ADENOSQUAMOUS CARCINOMA																				1
MIXED TUMOR, MALIGNANT																		X		3
UTERUS	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
LEIOMYOSARCOMA																	X			1
OVARY	+	+	+	+	+	+	+	+	+	A	+	+	+	-	+	+	-	-	+	44
NERVOUS SYSTEM																				
BRAIN	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
EPENDYMOMA																				1
MUSCULOSKELETAL SYSTEM																				
BONE	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	48*
OSTEOSARCOMA						X														1
ALL OTHER SYSTEMS																				
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	48*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			X					X												8
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																				1
MALIGNANT LYMPHOMA, MIXED TYPE		X					X													2

* 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 D-MANNITOL

LOW DOSE

ANIMAL NUMBER	00011	00021	00031	00041	00051	00061	00071	00081	00091	00101	00111	00121	00131	00141	00151	00161	00171	00181	00191	00201	00211	00221	00231	00241	00251
WEEKS ON STUDY	0900	0855	1005	1005	1005	1005	1005	1005	0904	1005	1005	1005	1005	1005	0105	1005	1101	0809	0805	1005	1005	1005	1005	1005	1005
INTEGUMENTARY SYSTEM																									
SKIN	+	A	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																									
SUBCUTANEOUS TISSUE	+	A	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
RHABDOMYOSARCOMA					X																				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																X									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	A	-	-	+	-	-	-	+	-	-	-	+	-	-	+	+	+	+	+	+	+	-	-	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
SPLEEN	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RHABDOMYOSARCOMA, METASTATIC																									
THYMUS	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
CIRCULATORY SYSTEM																									
HEART	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																									
HEPATOCELLULAR CARCINOMA											X														
HEMANGIOSARCOMA																									X
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
BILE DUCT	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	A	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+
PANCREAS	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ESOPHAGUS	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE											X														
LARGE INTESTINE	-	A	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																						X			
ADRENAL	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
PARATHYROID	-	A	+	+	+	+	+	+	-	+	-	+	+	+	-	-	+	+	-	+	+	+	+	+	+
PANCREATIC ISLETS	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	A	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
ADENOCA/SQUAMOUS METAPLASIA																									
UTERUS	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LUTEOMA																X									
NERVOUS SYSTEM																									
BRAIN	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	A	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																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	X															X									
MALIGNANT LYMPHOMA, MIXED TYPE										X		X													
LYMPHOCYTIC LEUKEMIA									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) 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	105	105	105	091	095	105	091	051	101	105	105	105	105	105	105	106	105	102	108	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	A	+	+	48*
HEMANGIOMA	X																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	A	+	+	48*
RHABDOMYOSARCOMA																						X				2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
ALVEOLAR/BRONCHIOLAR ADENOMA	X																									1
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	-	+	-	-	+	+	+	-	+	+	+	-	+	+	+	-	+	+	+	+	+	A	+	-	29
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	47
HEMANGIOSARCOMA					X																					1
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	47
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	A	+	+	47
RHABDOMYOSARCOMA, METASTATIC																						X				1
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	-	46
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	A	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
HEPATOCELLULAR ADENOMA																						X				1
HEPATOCELLULAR CARCINOMA																								X		2
HEMANGIOSARCOMA																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									X	1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	A	+	+	48
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	N	+	+	+	+	+	A	N	+	48*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	A	+	+	45
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	42
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	43
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	A	-	-	44
ADENOMA, NOS	X																									2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	-	47
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
FOLLICULAR-CELL CARCINOMA															X							X				2
PARATHYROID	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	-	+	+	-	+	-	A	-	+	35
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	A	+	+	45
ISLET-CELL CARCINOMA																	X									1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	A	+	+	48*
ADENOCARCINOMA, NOS																				X						1
ADENOCA/SQUAMOUS METAPLASIA																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
OVARY	+	+	+	+	+	-	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	A	-	+	44
LUTEOMA																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
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	A	N	N	48*
MALIGNANT LYMPHOMA, NOS																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			X																			X				2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE										X					X											4
MALIGNANT LYMPHOMA, MIXED TYPE									X																	2
LYMPHOCYTIC LEUKEMIA												X														2

* 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 D-MANNITOL

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	104	079	104	104	104	073	104	104	104	074	106	102	071	104	104	104	104	104	103	098	094	104	104	104	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	N	+	+	+	+	+	+	+
HEMANGIOMA																									X
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, METASTATIC																									
ALVEOLAR/BRONCHIOLAR ADENOMA																			X						
TRACHEA	-	+	-	+	-	+	+	-	+	+	-	+	A	-	+	+	+	+	+	+	+	+	-	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																								X	
LYMPH NODES	-	+	+	+	+	+	•	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	+	+	+	+	-	+	+	+	+	A	+	+	+	+	+	+	-	-	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	-	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA							X																		
HEPATOCELLULAR CARCINOMA																			•						
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	+	+	+	+	+	N	+	+	+	+	A	+	N	+	+	+	+	N	+	+	+	+	+
PANCREAS	+	-	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	-	-	+	+	+	+
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	-	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	-	+	+	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	-	+	+	+
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	-	-	-	-	-	-	+	-	+	-	+	-	A	-	+	-	-	-	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	N	+	+	+	+	+	+	+
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA															X										
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	-	+	+	-	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT RETICULOSIS																			X						
SPINAL CORD	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT RETICULOSIS																			Xa						
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																									
ADENOMA, NOS																									
CYSTADENOMA, NOS																			X						
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																					X				
MALIGNANT LYMPHOMA, MIXED TYPE																		X							
LYMPHOCYTIC LEUKEMIA		X								X															

a: MULTIPLE OCCURENCE OF MORPHOLOGY

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMIN ON
: 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 / WEEKS ON STUDY	0212 0910	0217 0904	0218 0904	0219 1104	0231 0104	0232 0104	0233 0104	0234 0104	0235 0104	0236 0104	0237 0104	0238 0104	0239 0104	0240 0104	0241 0104	0242 0104	0243 0104	0244 0104	0245 0104	0246 0104	0247 0104	0248 0104	0249 0104	0250 0104	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	49*
HEMANGIOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA, NOS, METASTATIC																			X						1
ALVEOLAR/BRONCHIOLAR ADENOMA																									1
TRACHEA	+	-	+	-	-	-	+	-	+	-	+	+	-	+	-	-	+	-	+	-	-	+	-	+	27
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA																									1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYMUS	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA																									1
HEPATOCELLULAR CARCINOMA																			X						1
HEMANGIOSARCOMA	X																								1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	N	+	+	+	+	+	N	+	49*
PANCREAS	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	+	+	45
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	47
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	44
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	+	44
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	47
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PHEOCHROMOCYTOMA						X																			1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																			X						1
PARATHYROID	-	+	+	+	-	+	-	+	-	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	30
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	N	+	N	49*
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA																									1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	46
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIGNANT RETICULOSIS																									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	49*
MALIGNANT RETICULOSIS																									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	49*
CARCINOMA,NOS																			X						1
ADENOMA, NOS										X															1
CYSTADENOMA, 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	49*
SARCOMA, NOS																							X		1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE								X																	1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									1
MALIGNANT LYMPHOMA, MIXED TYPE																									1
LYMPHOCYTIC LEUKEMIA											X										X				4

* 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 C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED DIETS CONTAINING D-MANNITOL

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DIETS CONTAINING D-MANNITOL

	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	4 (8%)	1 (2%)	6 (12%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)
PARAKERATOSIS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(50)	(50)
HYPERPLASIA, NOS	2 (4%)		
#LUNG	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	2 (4%)
LIPOGRANULOMA	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#SPLEEN	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
FIBROSIS, FOCAL	1 (2%)	2 (4%)	1 (2%)
INFARCT, NOS	1 (2%)		1 (2%)
HEMOSIDEROSIS			1 (2%)
HYPERPLASIA, FOCAL	1 (2%)		
HEMATOPOIESIS	3 (6%)	1 (2%)	2 (4%)
#LYMPH NODE	(50)	(50)	(50)
HYPERPLASIA, 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
#MANDIBULAR L. NODE	(50)	(50)	(50)
CYST, NOS			2 (4%)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
HYPERPLASIA, CYSTIC	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID		2 (4%)	
#MEDIASTINAL L.NODE	(50)	(50)	(50)
ANGIECTASIS		1 (2%)	
#PANCREATIC L.NODE	(50)	(50)	(50)
ANGIECTASIS		1 (2%)	
#LUNG	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	1 (2%)	2 (4%)	
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	5 (10%)	2 (4%)	3 (6%)
HEMATOPOIESIS		1 (2%)	
#KIDNEY	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	2 (4%)		
#THYMUS	(40)	(40)	(38)
CYST, NOS			1 (3%)
HYPERPLASIA, CYSTIC			1 (3%)
CIRCULATORY SYSTEM			
#CEREBRAL BASAL SURFA	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIARTERITIS		1 (2%)	1 (2%)
#PANCREATIC L.NODE	(50)	(50)	(50)
LYMPHANGIECTASIS			1 (2%)
#HEART	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)	
FIBROSIS, DIFFUSE		1 (2%)	
#HEART/ATRIUM	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)	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
#LEFT ATRIUM	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		2 (4%)
FIBROSIS, FOCAL	4 (8%)	8 (16%)	1 (2%)
FIBROSIS, DIFFUSE	1 (2%)	4 (8%)	1 (2%)
*PANCREATIC ARTERY	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
#PANCREAS	(50)	(50)	(50)
PERIARTERITIS		1 (2%)	
#GASTRIC SEROSA	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
*MESENTERY	(50)	(50)	(50)
PERIARTERITIS	2 (4%)	1 (2%)	2 (4%)
DIGESTIVE SYSTEM			
*INTESTINAL TRACT	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
#PAROTID GLAND	(49)	(49)	(49)
ATROPHY, FOCAL		1 (2%)	
#LIVER	(50)	(50)	(50)
CONGESTION, NOS		2 (4%)	
HEMORRHAGE	1 (2%)		
ADHESION, FIBROUS			1 (2%)
DEGENERATION, CYSTIC	3 (6%)		
NECROSIS, FOCAL	3 (6%)		
NECROSIS, COAGULATIVE		1 (2%)	1 (2%)
METAMORPHOSIS FATTY		1 (2%)	1 (2%)
HEMOSIDEROSIS	1 (2%)		
CYTOPLASMIC VACUOLIZATION	8 (16%)	4 (8%)	4 (8%)
NODULAR REGENERATION	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
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
NECROSIS, NOS	1 (2%)		
METAMORPHOSIS FATTY	4 (8%)		2 (4%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		1 (2%)
ATROPHY, NOS	3 (6%)	3 (6%)	
#LIVER/PERIPORTAL	(50)	(50)	(50)
METAMORPHOSIS FATTY	1 (2%)		
HISTIOCYTOSIS		1 (2%)	
#LIVER/HEPATOCYTES	(50)	(50)	(50)
DEGENERATION, CYSTIC		3 (6%)	
CYTOPLASMIC VACUOLIZATION		1 (2%)	
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	31 (62%)	37 (74%)	37 (74%)
HYPERPLASIA, CYSTIC	1 (2%)		
#PANCREAS	(50)	(50)	(50)
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, FOCAL			1 (2%)
#PANCREATIC DUCT	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			2 (4%)
#PANCREATIC ACINUS	(50)	(50)	(50)
FIBROSIS, FOCAL	1 (2%)		
ATROPHY, NOS	2 (4%)		3 (6%)
ATROPHY, FOCAL	7 (14%)	14 (28%)	5 (10%)
#GASTRIC MUCOSA	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
ULCER, NOS		1 (2%)	3 (6%)
CALCIFICATION, FOCAL			1 (2%)
HYPERTROPHY, NOS	1 (2%)		
#GASTRIC FUNDAL GLAND	(50)	(50)	(50)
DILATATION, NOS	4 (8%)	9 (18%)	3 (6%)
#GASTRIC SUBMUCOSA	(50)	(50)	(50)
EDEMA, NOS			1 (2%)
#SMALL INTESTINE	(50)	(49)	(50)
METAPLASIA, OSSEOUS			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CYST, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
NEPHROSIS, NOS	45 (90%)	42 (84%)	42 (84%)
#KIDNEY/TUBULE	(50)	(50)	(50)
PIGMENTATION, NOS		1 (2%)	
#URINARY BLADDER	(50)	(50)	(49)
MUCOCELE			1 (2%)
#U. BLADDER/MUCOSA	(50)	(50)	(49)
NECROSIS, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(50)	(50)
HYPERPLASIA, NOS	3 (7%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
#ANTERIOR PITUITARY	(46)	(50)	(50)
CYST, NOS			1 (2%)
HEMORRHAGIC CYST	1 (2%)		
HEMOSIDEROSIS		1 (2%)	
#ADRENAL	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(50)
HEMORRHAGIC CYST			1 (2%)
METAMORPHOSIS FATTY		1 (2%)	
CYTOPLASMIC CHANGE, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION	7 (14%)	5 (10%)	1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)
CYTOPLASMIC CHANGE, NOS	1 (2%)		
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL	5 (10%)	2 (4%)	3 (6%)
ANGIECTASIS		1 (2%)	
#THYROID	(49)	(50)	(50)
THYROGLOSSAL DUCT CYST			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

CYSTIC FOLLICLES	2 (4%)		2 (4%)
DEGENERATION, CYSTIC	2 (4%)	7 (14%)	7 (14%)
HYPERPLASIA, C-CELL	6 (12%)	7 (14%)	4 (8%)
#PANCREATIC ISLETS	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	1 (2%)	5 (10%)	1 (2%)
HEMORRHAGIC CYST		1 (2%)	
REACTION, FOREIGN BODY		1 (2%)	
PIGMENTATION, NOS		1 (2%)	
HYPERPLASIA, CYSTIC		1 (2%)	
ADENOSIS		1 (2%)	
CYSTIC DISEASE	17 (34%)	8 (16%)	8 (16%)
*MAMMARY DUCT	(50)	(50)	(50)
HEMORRHAGIC CYST			1 (2%)
REACTION, FOREIGN BODY		1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	4 (8%)
HYPERPLASIA, CYSTIC	1 (2%)		3 (6%)
#PROSTATE	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, SUPPURATIVE	20 (40%)	31 (62%)	30 (60%)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
DEGENERATION, CYSTIC		1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	
#TESTIS	(50)	(50)	(50)
ATROPHY, NOS	30 (60%)	37 (74%)	33 (66%)
HYPERPLASIA, INTERSTITIAL CELL	2 (4%)	2 (4%)	1 (2%)
*EPIDIDYMIS	(50)	(50)	(50)
GRANULOMA, SPERMATIC	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

NECROSIS, FOCAL	1 (2%)		1 (2%)
#CEREBRAL BASAL SURFA	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#BRAIN/THALAMUS	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
NECROSIS, FOCAL		1 (2%)	
#HYPOTHALAMUS	(50)	(50)	(50)
COMPRESSION	1 (2%)	2 (4%)	2 (4%)
#PONS	(50)	(50)	(50)
COMPRESSION	1 (2%)		
#CEREBELLUM	(50)	(50)	(50)
PSAMMOMA BODIES			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE	3 (6%)		1 (2%)
RETINOPATHY	17 (34%)	6 (12%)	42 (84%)
CATARACT	15 (30%)	6 (12%)	40 (80%)
*EYE/CORNEA	(50)	(50)	(50)
PERFORATING WOUND	1 (2%)		
FOREIGN BODY, NOS	1 (2%)		
INFLAMMATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
FIBROSIS, FOCAL		1 (2%)	
NECROSIS, FAT	6 (12%)	5 (10%)	
ALL OTHER SYSTEMS			
LEG			
HEMATOMA, NOS	1		
OMENTUM			
NECROSIS, FAT	3	2	1
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 D-MANNITOL

	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)
ULCER, CHRONIC	1 (2%)		1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(49)	(50)
HYPERPLASIA, NOS	2 (4%)		3 (6%)
HYPERPLASIA, ADENOMATOUS	2 (4%)		
#LUNG	(50)	(49)	(50)
CONGESTION, NOS		1 (2%)	1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	3 (6%)		4 (8%)
HISTIOCYTOSIS			1 (2%)
#ALVEOLAR EPITHELIUM	(50)	(49)	(50)
HYPERPLASIA, ADENOMATOUS	2 (4%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(50)	(50)
MYELOFIBROSIS		2 (4%)	
#SPLEEN	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
HEMATOPOIESIS	1 (2%)	2 (4%)	1 (2%)
#LYMPH NODE	(49)	(50)	(50)
HYPERPLASIA, 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
#MANDIBULAR L. NODE	(49)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, CYSTIC	3 (6%)		
#MESENTERIC L. NODE	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#INGUINAL LYMPH NODE	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LUNG	(50)	(49)	(50)
LEUKOCYTOSIS, NOS		1 (2%)	
HEMATOPOIESIS		1 (2%)	1 (2%)
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	5 (10%)		
HEMATOPOIESIS		1 (2%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, INTERSTITIAL		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
FIBROSIS, FOCAL	2 (4%)	3 (6%)	2 (4%)
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#PANCREAS	(50)	(49)	(49)
PERIARTERITIS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
DEFORMITY, NOS	2 (4%)		
NECROSIS, COAGULATIVE		2 (4%)	
CYTOPLASMIC CHANGE, NOS	1 (2%)		
CYTOPLASMIC VACUOLIZATION		4 (8%)	3 (6%)
BASOPHILIC CYTO CHANGE	33 (66%)	32 (64%)	44 (88%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

CYTOLOGIC ALTERATION, NOS	1 (2%)		
NODULAR REGENERATION		1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
METAMORPHOSIS FATTY		2 (4%)	
CYTOPLASMIC VACUOLIZATION		1 (2%)	1 (2%)
ATROPHY, NOS		1 (2%)	
#LIVER/PERIPORTAL	(50)	(50)	(50)
METAMORPHOSIS FATTY	1 (2%)	1 (2%)	
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	43 (86%)	40 (80%)	49 (98%)
HYPERPLASIA, FOCAL			1 (2%)
#PANCREAS	(50)	(49)	(49)
ATROPHY, FOCAL			1 (2%)
#PANCREATIC ACINUS	(50)	(49)	(49)
ATROPHY, NOS	2 (4%)		
ATROPHY, FOCAL	5 (10%)	2 (4%)	2 (4%)
#GASTRIC MUCOSA	(50)	(50)	(50)
ULCER, NOS	1 (2%)		
#GASTRIC FUNDAL GLAND	(50)	(50)	(50)
DILATATION, NOS	6 (12%)	23 (46%)	23 (46%)
#PEYER'S PATCH	(50)	(50)	(49)
INFLAMMATION, NOS			1 (2%)
#COLON	(50)	(50)	(49)
NEMATODIASIS			1 (2%)
#COLONIC CRYPT OF LIE	(50)	(50)	(49)
DILATATION, NOS		2 (4%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CYST, NOS			1 (2%)
GLOMERULONEPHRITIS, NOS			1 (2%)
NEPHROSIS, NOS	29 (58%)	10 (20%)	12 (24%)
#KIDNEY/CORTEX	(50)	(50)	(50)
PIGMENTATION, NOS			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

#KIDNEY/TUBULE	(50)	(50)	(50)
PIGMENTATION, NOS		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(47)	(48)
HYPERPLASIA, NOS	5 (10%)	2 (4%)	2 (4%)
#ANTERIOR PITUITARY	(50)	(47)	(48)
ANGIECTASIS	2 (4%)	2 (4%)	2 (4%)
#ADRENAL	(49)	(50)	(50)
CYTOPLASMIC VACUOLIZATION		1 (2%)	
#ADRENAL CORTEX	(49)	(50)	(50)
HEMORRHAGE		1 (2%)	
CYTOPLASMIC VACUOLIZATION	11 (22%)	7 (14%)	9 (18%)
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(49)	(50)	(50)
HYPERPLASIA, FOCAL			4 (8%)
#THYROID	(50)	(50)	(50)
ULTIMOBRANCHIAL CYST	2 (4%)		
DEGENERATION, CYSTIC	1 (2%)		
ATROPHY, FOCAL			1 (2%)
HYPERPLASIA, CYSTIC	1 (2%)		
HYPERPLASIA, C-CELL	3 (6%)	5 (10%)	5 (10%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	2 (4%)	3 (6%)	1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
HYPERPLASIA, CYSTIC	3 (6%)	5 (10%)	1 (2%)
ADENOSIS		1 (2%)	2 (4%)
CYSTIC DISEASE	35 (70%)	36 (72%)	40 (80%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CYST, NOS	1 (2%)		
EPIDERMAL INCLUSION CYST			1 (2%)
CYSTIC DUCTS		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

INFLAMMATION, SUPPURATIVE	2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	1 (2%)	2 (4%)	2 (4%)
*VAGINA	(50)	(50)	(50)
DISPLACEMENT, NOS		1 (2%)	
#UTERUS	(50)	(50)	(50)
HYDROMETRA		1 (2%)	2 (4%)
INFLAMMATION, SUPPURATIVE			1 (2%)
DECIDUAL ALTERATION, NOS			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
CYST, NOS	1 (2%)		
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, CYSTIC	2 (4%)	1 (2%)	2 (4%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
#ENDOMETRIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS	1 (2%)		
#OVARY	(50)	(50)	(50)
CYST, NOS	1 (2%)		
FOLLICULAR CYST, NOS	1 (2%)		3 (6%)
CORPUS LUTEUM CYST		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
METAPLASIA, OSSEOUS		1 (2%)	
#HYPOTHALAMUS	(50)	(50)	(50)
COMPRESSION	10 (20%)	3 (6%)	2 (4%)
#PONS	(50)	(50)	(50)
COMPRESSION			1 (2%)
*WHITE MATTER SPINAL	(50)	(50)	(50)
DEGENERATION, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE		2 (4%)	1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

RETINOPATHY	10 (20%)	43 (86%)	33 (66%)
CATARACT	9 (18%)	40 (80%)	32 (64%)
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(50)	(50)
HYPEROSTOSIS			1 (2%)
*MUSCLE OF BACK	(50)	(50)	(50)
FIBROSIS		1 (2%)	
BODY CAVITIES			
*ABDOMINAL WALL	(50)	(50)	(50)
NECROSIS, FAT		1 (2%)	
*MESENTERY	(50)	(50)	(50)
HEMATOMA, NOS			1 (2%)
LIPOGRANULOMA		1 (2%)	
NECROSIS, FAT	8 (16%)	7 (14%)	3 (6%)
ALL OTHER SYSTEMS			
DIAPHRAGM			
NECROSIS, FAT		1	
OMENTUM			
NECROSIS, FAT	4	1	1
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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 D-MANNITOL

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED DIETS CONTAINING D-MANNITOL

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)	11 (22%)	
ULCER, CHRONIC	4 (8%)	1 (2%)	1 (2%)
FIBROSIS	1 (2%)		
KELOID		3 (6%)	1 (2%)
HYPERPLASIA, FOCAL	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(49)
INFLAMMATION, CHRONIC	2 (4%)		
INFLAMMATION, GRANULOMATOUS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)	4 (8%)	
#LUNG	(50)	(50)	(49)
CONGESTION, NOS	1 (2%)	1 (2%)	4 (8%)
INFLAMMATION, INTERSTITIAL		1 (2%)	
INFLAMMATION, GRANULOMATOUS			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	9 (18%)	8 (16%)	20 (41%)
PROTEINOSIS, ALVEOLAR		1 (2%)	
HYPERPLASIA, ADENOMATOUS	11 (22%)	10 (20%)	26 (53%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	4 (8%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

#BONE MARROW	(47)	(48)	(46)
HYPERPLASIA, LYMPHOID	1 (2%)		
HYPOPLASIA, HEMATOPOIETIC	1 (2%)		
#SPLEEN	(49)	(49)	(47)
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	4 (8%)	3 (6%)	9 (19%)
#MANDIBULAR L. NODE	(49)	(50)	(47)
MASTOCYTOSIS		1 (2%)	
#PANCREATIC L.NODE	(49)	(50)	(47)
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(49)	(50)	(47)
INFLAMMATION, SUPPURATIVE			1 (2%)
ANGIECTASIS	7 (14%)	2 (4%)	
HYPERPLASIA, LYMPHOID			1 (2%)
HEMATOPOIESIS	4 (8%)		2 (4%)
#LUNG	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS		1 (2%)	
#PEYER'S PATCH	(45)	(47)	(47)
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#BRAIN	(50)	(50)	(49)
PERIARTERITIS			1 (2%)
#HEART	(50)	(50)	(49)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
*MESENTERY	(50)	(50)	(49)
PERIARTERITIS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
CYST, NOS	1 (2%)	1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

INFLAMMATION, FOCAL		1 (2%)	1 (2%)
INFLAMMATION, MULTIFOCAL	2 (4%)		
NECROSIS, COAGULATIVE	1 (2%)		
INFARCT, NOS	2 (4%)		
METAMORPHOSIS FATTY			1 (2%)
CALCIFICATION, NOS		1 (2%)	
CYTOPLASMIC VACUOLIZATION	2 (4%)		1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(49)
CYTOPLASMIC VACUOLIZATION	1 (2%)	4 (8%)	5 (10%)
#BILE DUCT	(50)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)		
#PANCREAS	(48)	(49)	(47)
CYSTIC DUCTS		2 (4%)	1 (2%)
INFLAMMATION, CHRONIC		2 (4%)	
#PEYER'S PATCH	(45)	(47)	(47)
INFLAMMATION, NOS			1 (2%)
*RECTUM	(50)	(50)	(49)
PROLAPSE		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
ULCER, CHRONIC		1 (2%)	
*ANUS	(50)	(50)	(49)
INFLAMMATION, CHRONIC		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(47)
INFLAMMATION, SUPPURATIVE	1 (2%)		
NEPHROSIS, NOS	15 (30%)	29 (58%)	30 (64%)
#KIDNEY/TUBULE	(50)	(50)	(47)
DILATATION, NOS		1 (2%)	
#U.BLADDER/SUBMUCOSA	(48)	(50)	(46)
FIBROSIS	1 (2%)		
ENDOCRINE SYSTEM			
#THYROID	(50)	(50)	(47)
DEGENERATION, CYSTIC	7 (14%)	8 (16%)	6 (13%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

#PARATHYROID	(34)	(28)	(27)
HYPERPLASIA, NOS	1 (3%)		
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(50)	(49)
CYSTIC DUCTS			2 (4%)
INFLAMMATION, SUPPURATIVE	2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV		2 (4%)	
*EPIDIDYMIS	(50)	(50)	(49)
INFLAMMATION, CHRONIC			1 (2%)
NERVOUS SYSTEM			
#CEREBRUM	(50)	(50)	(49)
HEMORRHAGE	1 (2%)		
#BRAIN/THALAMUS	(50)	(50)	(49)
PSAMMOMA BODIES	9 (18%)	13 (26%)	17 (35%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(50)	(49)
STEATITIS	1 (2%)		1 (2%)
NECROSIS, FAT		1 (2%)	3 (6%)
ALL OTHER SYSTEMS			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

SPECIAL MORPHOLOGY SUMMARY

NO LESION REPORTED	3	2	1
AUTOLYSIS/NO NECROPSY			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 D-MANNITOL

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	48	49
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(48)	(49)
FIBROSIS, DIFFUSE		1 (2%)	
RESPIRATORY SYSTEM			
*LARYNGEAL GLAND	(48)	(48)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)
#TRACHEAL GLAND	(31)	(29)	(27)
INFLAMMATION, SUPPURATIVE		1 (3%)	
#LUNG/BRONCHIOLE	(48)	(48)	(49)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
#LUNG	(48)	(48)	(49)
CONGESTION, NOS			2 (4%)
INFLAMMATION, INTERSTITIAL			1 (2%)
PNEUMONIA, ASPIRATION			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	7 (15%)	14 (29%)	14 (29%)
HYPERPLASIA, ADENOMATOUS	10 (21%)	19 (40%)	16 (33%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(48)	(49)
LEUKEMOID REACTION	1 (2%)		
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)	6 (13%)	1 (2%)
HEMATOPOIESIS			1 (2%)
*MEDIASTINUM	(48)	(48)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

#SPLEEN	(48)	(47)	(48)
HYPERPLASIA, LYMPHOID	1 (2%)	5 (11%)	7 (15%)
HEMATOPOIESIS	4 (8%)	5 (11%)	5 (10%)
#SPLENIC RED PULP	(48)	(47)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	
#BRONCHIAL LYMPH NODE	(48)	(47)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(48)	(47)	(48)
NECROSIS, FOCAL		1 (2%)	
ANGIECTASIS		1 (2%)	
HYPERPLASIA, LYMPHOID		3 (6%)	1 (2%)
HEMATOPOIESIS			1 (2%)
#RENAL LYMPH NODE	(48)	(47)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
#INGUINAL LYMPH NODE	(48)	(47)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
#LUNG	(48)	(48)	(49)
HYPERPLASIA, LYMPHOID		2 (4%)	2 (4%)
#LIVER	(48)	(48)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
HEMATOPOIESIS			3 (6%)
#KIDNEY	(48)	(48)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
#URINARY BLADDER	(47)	(48)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#OVARY	(44)	(44)	(46)
HYPERPLASIA, LYMPHOID	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(48)	(48)	(48)
ENDOCARDITIS, BACTERIAL	1 (2%)		
#MYOCARDIUM	(48)	(48)	(48)
INFLAMMATION, SUPPURATIVE	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

PERIARTERITIS			1 (2%)
#UTERUS	(47)	(48)	(49)
PERIARTERITIS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(48)	(48)	(49)
INFLAMMATION, FOCAL	2 (4%)	2 (4%)	2 (4%)
INFLAMMATION, MULTIFOCAL	2 (4%)	4 (8%)	15 (31%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
CHOLANGIOFIBROSIS		1 (2%)	
NECROSIS, COAGULATIVE		2 (4%)	1 (2%)
CYTOPLASMIC CHANGE, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION		2 (4%)	1 (2%)
#LIVER/PERIPORTAL	(48)	(48)	(49)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
#BILE DUCT	(48)	(48)	(49)
DEGENERATION, HYALINE		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
#PANCREAS	(48)	(45)	(45)
CYSTIC DUCTS	1 (2%)	1 (2%)	1 (2%)
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
ATROPHY, FOCAL		1 (2%)	
#COLON	(46)	(43)	(44)
NEMATODIASIS			1 (2%)
#COLONIC SUBMUCOSA	(46)	(43)	(44)
INFLAMMATION, SUPPURATIVE	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(48)	(48)	(49)
INFLAMMATION, CHRONIC	1 (2%)		
NEPHROSIS, NOS	1 (2%)	3 (6%)	14 (29%)
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(44)	(47)
HEMORRHAGIC CYST			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

HYPERPLASIA, NOS			1 (2%)
#ADRENAL	(48)	(47)	(48)
DEGENERATION, NOS	1 (2%)		
#ADRENAL CORTEX	(48)	(47)	(48)
EOSINOPHILIC CYTO CHANGE		1 (2%)	
#THYROID	(46)	(48)	(49)
DEGENERATION, CYSTIC	4 (9%)	6 (13%)	9 (18%)
ATROPHY, SENILE	3 (7%)		
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(48)	(48)	(49)
CYSTIC DUCTS	1 (2%)		4 (8%)
*VAGINA	(48)	(48)	(49)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#UTERUS	(47)	(48)	(49)
HYDROMETRA			2 (4%)
INFLAMMATION, SUPPURATIVE	3 (6%)		13 (27%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
#UTERUS/ENDOMETRIUM	(47)	(48)	(49)
INFLAMMATION, SUPPURATIVE	2 (4%)	3 (6%)	2 (4%)
ABSCESS, NOS	1 (2%)		1 (2%)
DEGENERATION, CYSTIC		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, CYSTIC	35 (74%)	42 (88%)	35 (71%)
METAPLASIA, SQUAMOUS			1 (2%)
#UTERUS/MYOMETRIUM	(47)	(48)	(49)
ANGIECTASIS		1 (2%)	
#OVARY	(44)	(44)	(46)
FOLLICULAR CYST, NOS	4 (9%)	9 (20%)	11 (24%)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	2 (4%)
ABSCESS, NOS			2 (4%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)	1 (2%)	3 (7%)
ABSCESS, CHRONIC	1 (2%)	1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

INFLAMMATION, GRANULOMATOUS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(48)	(48)	(49)
DEGENERATION, NOS		1 (2%)	
CHOLESTEROL DEPOSIT		1 (2%)	
#BRAIN/THALAMUS	(48)	(48)	(49)
PSAMMOMA BODIES	7 (15%)	19 (40%)	12 (24%)
#HYPOTHALAMUS	(48)	(48)	(49)
COMPRESSION		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(48)	(48)	(49)
INFLAMMATION, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(48)	(48)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	1 (2%)
*MESENTERY	(48)	(48)	(49)
STEATITIS		1 (2%)	1 (2%)
NECROSIS, FAT		1 (2%)	4 (8%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(48)	(48)	(49)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, SUPPURATIVE			2 (4%)
BROAD LIGAMENT			
HEMORRHAGE		1	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		
AUTOLYSIS/NO NECROPSY	2	2	1

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

APPENDIX E

ANALYSIS OF D-MANNITOL (MIDWEST RESEARCH INSTITUTE)

APPENDIX E

A. ELEMENTAL ANALYSIS

Element	C	H	O
Theory	39.56	7.74	52.70
Determined			
1. Lot No. 4644:	39.84	7.78	
	39.72	7.79	
2. Lot No. 00041:	40.04	7.83	
	40.08	7.67	
3. Lot No. 20022:	39.42	7.71	53.11
	39.64	7.65	53.01

B. WATER ANALYSIS (Karl Fischer)

1. Lot No. 4644: $0.1614 \pm 0.0002(\delta)\%$
2. Lot No. 00041: $1.89 \pm 0.48(\delta)\%$
3. Lot No. 20022: $0.26 \pm 0.05(\delta)\%$

C. TITRATION WITH THIOSULFATE AFTER PERIODATE REACTION WITH MANNITOL

(U.S. Pharmacopeia, 1975)

1. Lot No. 4644: $100.5 \pm 0.6(\delta)\%$
2. Lot No. 000441: $97.8 \pm 0.7(\delta)\%$ (corrected for 1.89% water)
3. Lot No. 20022: $99.0 \pm 0.4(\delta)\%$ (corrected for 0.26% water)

D. MELTING POINT (Lot No. 4644)

Determined	Literature Values(Marti, 1930)
166° - 168°C (visual, capillary)	165.99°C
166° - 170°C (Du Pont 900DTA)	

E. OPTICAL ROTATION (Lot No. 4644)

Determined	Literature Values (Richtmyer and Hudson, 1951)
$[\alpha]_D^{28°} = + 18.3° \pm 0.3° (\delta)$	$[\alpha]_D^{20°} = + 14.9°$
C = 0.4 mg/ml in 5% aqueous ammonium molybdate	C = 0.4 mg/ml in 5% aqueous ammonium molybdate
$[\alpha]_D^{28°} = + 129.2° \pm 0.8° (\delta)$	$[\alpha]_D^{20°} = + 140.3°$
C = 0.4 mg/ml in 5% acidified aqueous ammonium molybdate	C = 0.32 mg/ml in 5% acidified aqueous ammonium molybdate

F. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel 60 F-254

Ref. Standard: D-Glucose

Amount Spotted: 35 and 70 μg

Visualization: 0.5% $KMnO_4$ in 1N NaOH

1. System 1 - Butanol:water (90:10), unsaturated tank
   Lot No. 4644: $R_f = 0.20$
   R_{st} □ 0.87

2. System 2 - 95% ethanol:water:ammonium hydroxide (77:15:8)
   Lot No. 4644: R_f = 0.39
   R_{st} = 1.1
   Lot No. 20022: R_f = 0.44
   R_{st} = 1.08

3. System 3 - Isobutanol:water (90:10)
   Lot No. 00041: R_f □ 0.11
   R_{st} = 0.81
   Lot no. 20022: R_f = 0.13
   R_{st} □ 0.79

4. System 4 - Ethanol:water:ammonium hydroxide (60:12:6)
   Lot No. 00041: R_f = 0.27
   R_{st} = 1.2

G. VAPOR-PHASE CHROMATOGRAPHY

Instrument: Tracor MT220

Detector: Flame ionization

Column: 10% UCW-98, 1.8 m x 4 mm I.D.

Oven Temperature Program: 100°-250°C at 10°C/minute

Preparation of Sample: The silyl derivative was prepared by adding the contents of a freshly opened 1-ml vial of "Tri-sil Z" (Pierce Chemical Co.) to 10-12 mg mannitol. The container was tightly capped and shaken vigorously for a minute in a water bath at 60°-70°C. The mannitol completely dissolved, and the resulting solution was injected on a gas chromatograph.

Lot No. 4644: Results: Major peak and one impurity

Peak	Retention Time (minutes)	Retention Time (Relative to Mannitol Derivative)	Area (Relative to Mannitol Derivative)
1	12.5	1.00	100
2	13.8	1.10	0.2

H. SPECTRAL DATA

	Methods	Results
1. Infrared		
a. Lot No. 4644	Instrument: Beckman IR-12 Cell: 1.5% KBr pellet	See Figure 5. Consistent with literature spectrum (Sadtler Standard Spectra)
b. Lot No. 00041 and Lot No. 20022	Instrument: Beckman IR-12 Cell: 1% KBr pellet	See Figures 6 and 7. Consistent with literature spectrum (Sadtler Standard Spectra)

	Methods	Results
2. Ultraviolet/Visible All three batches	Instrument: Cary 118 Solvent: Water	No maxima between 215 and 350 nm (ultraviolet range). No absorbance between 350 and 800 nm (visible range) at a concentration of 2 mg/ml. No literature value found. Spectra consistent with those expected for the structure.
3. Nuclear Magnetic Resonance a. Lot No. 4644	Instrument: Varian HA-100 Solvent: D_2O with internal sodium 3-trimethylsilyl propionate - 2,2,3,3-d_4	Assignments: See Figure 8. (1) m, δ 3.57 to 4.00 ppm (2) s, δ 4.75 ppm Integration Ratios: (1) 8.00 (2) HDO, -OH Consistent with literature spectrum (Sadtler Standard Spectra)
b. Lot No. 00041	Instrument: Varian EM-360 60 MHz Solvent: D_2O with internal sodium 3-trimethylsilyl propionate - 2,2,3,3-d_4	Assignments: See Figure 9. (1) m, δ 3.48 to 4.03 ppm (2) s, δ 4.77 ppm Integration Ratios: (1) 8.00 (2) HDO, -OH Consistent with literature spectrum (Sadtler Standard Spectra)
c. Lot No. 20022	Instrument: Varian EM 360-A Solvent: D_2O with internal sodium 3-trimethylsilyl propionate - 2,2,3,3-d_4	Assignments: See Figure 10. (1) m, δ 3.35 to 4.07 ppm (2) s, δ 4.78 ppm Integration Ratios: (1) 8.00 (2) HDO, -OH Consistent with literature reference (Sadtler Standard Spectra)

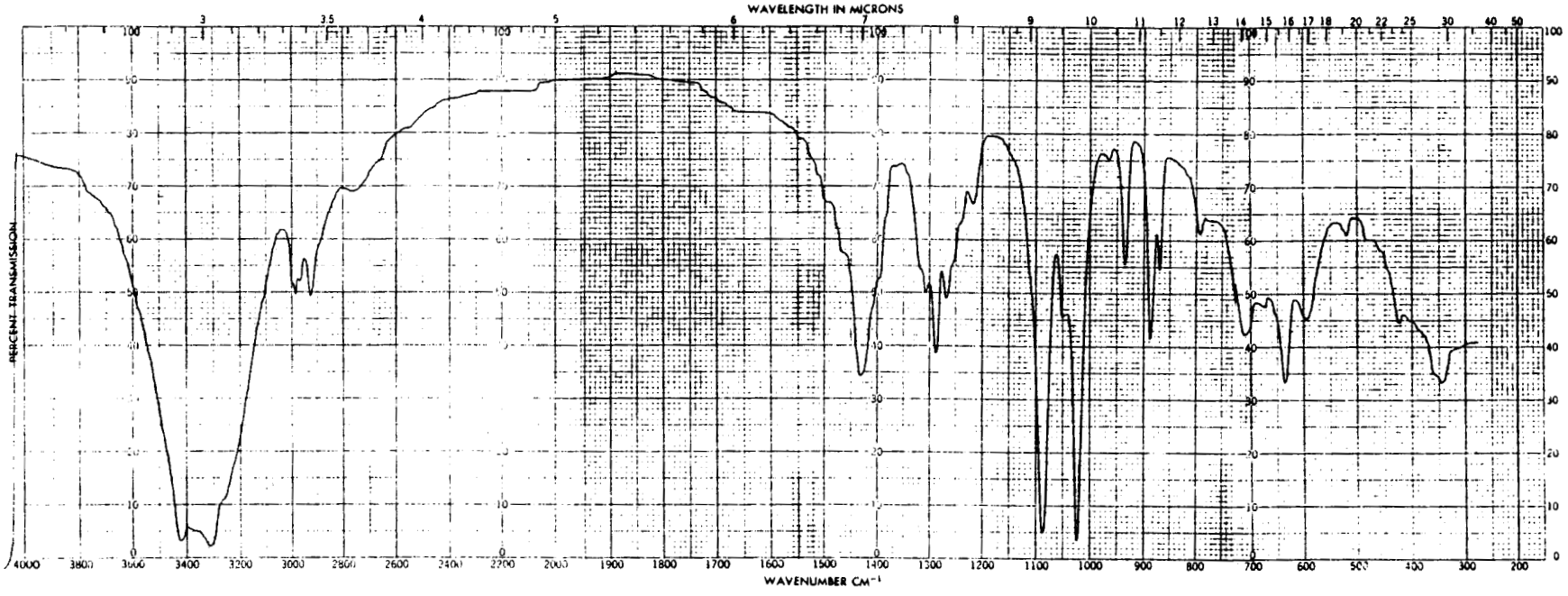

Figure 5. Infrared Absorption Spectrum of D-Mannitol (Lot No. 4644)

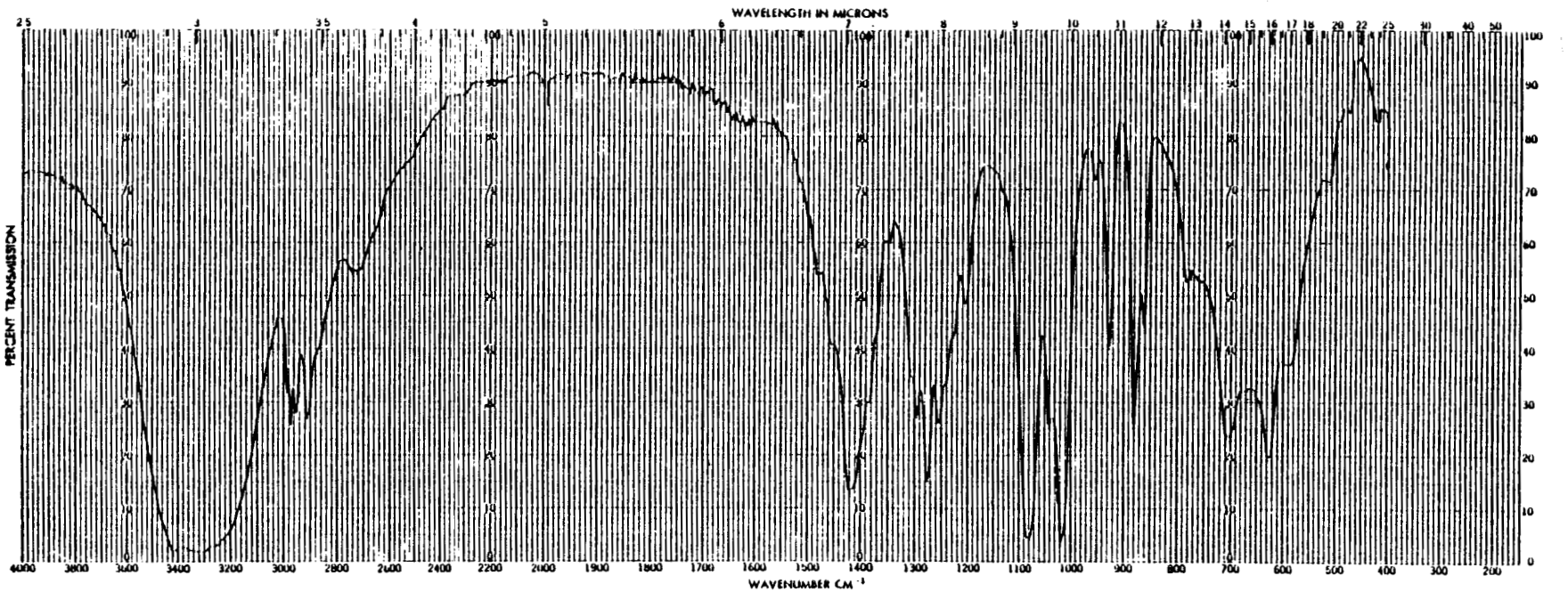

Figure 6. Infrared Absorption Spectrum of D-Mannitol (Lot No. 00041)

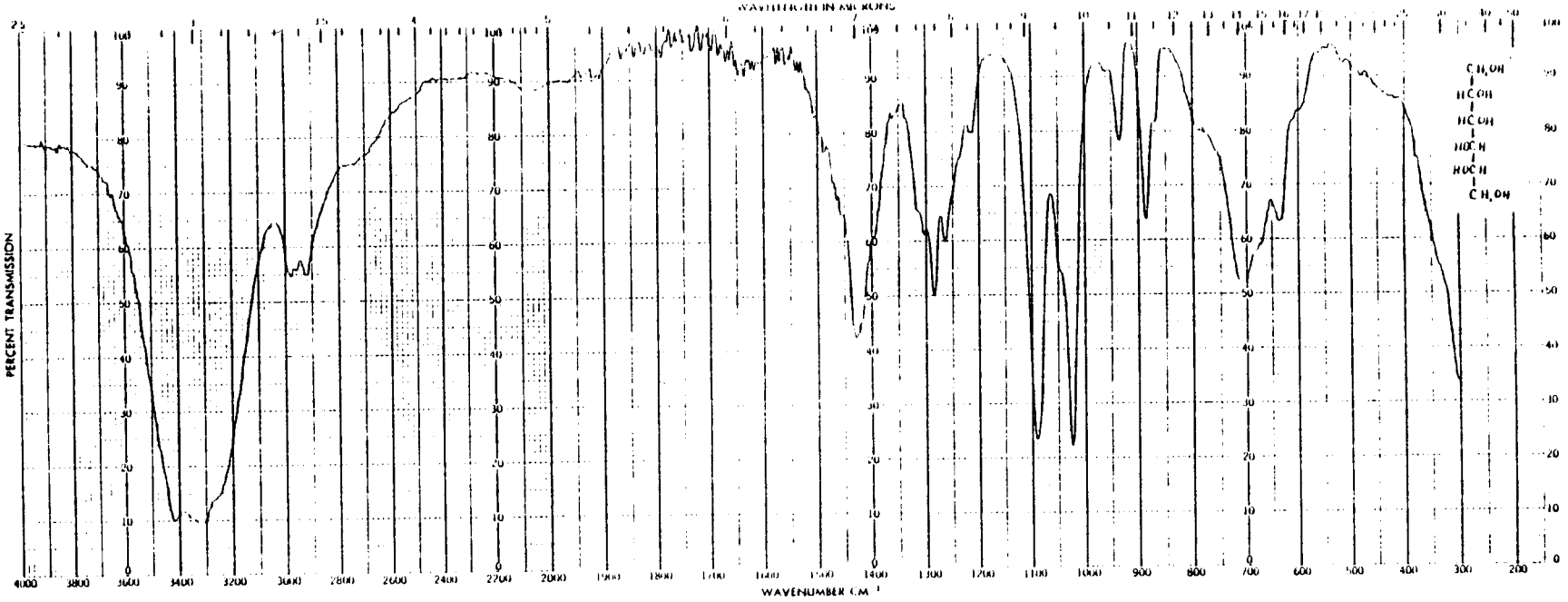

Figure 7. Infrared Absorption Spectrum of D-Mannitol (Lot No. 20022)

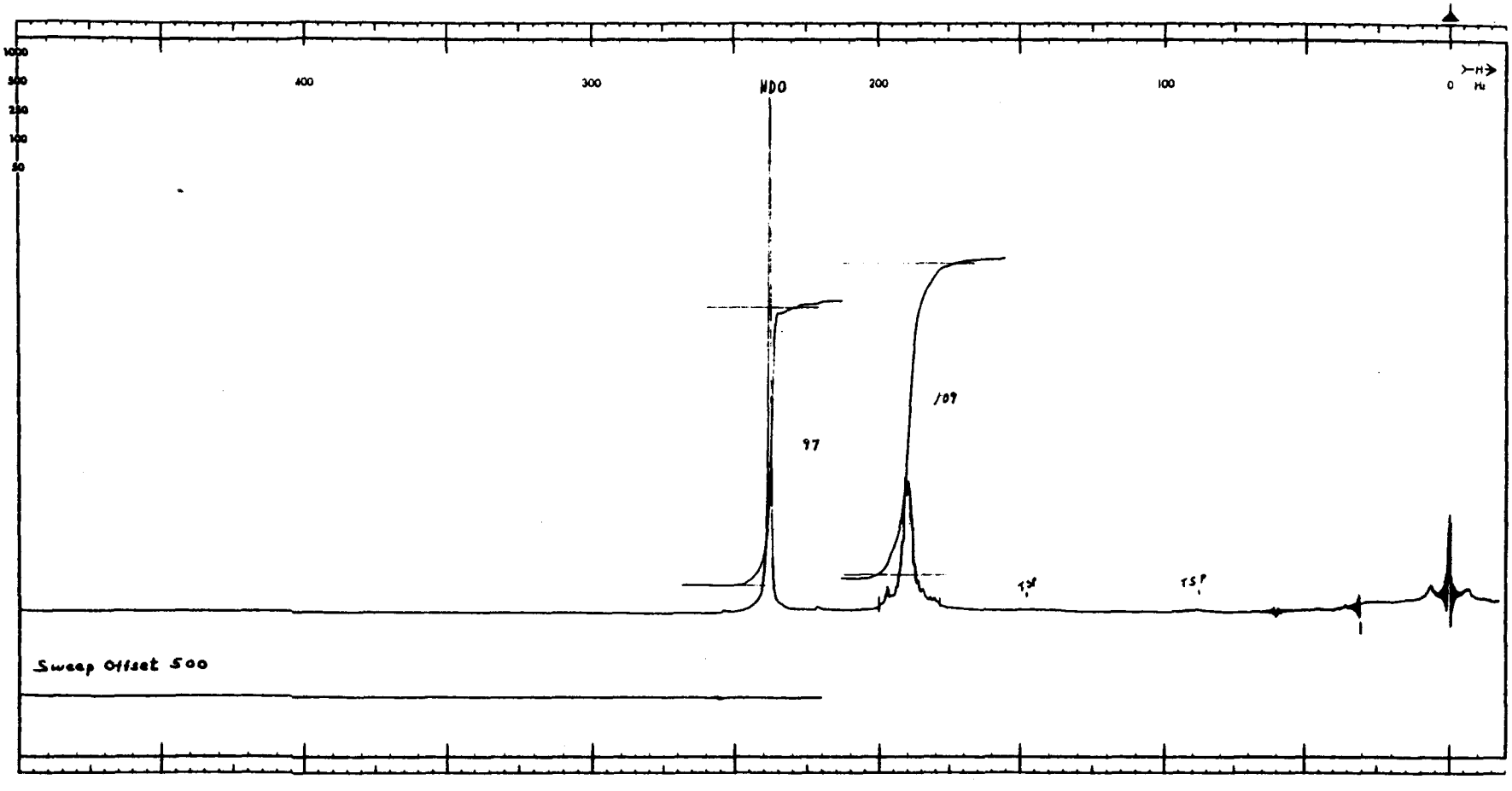

Figure 8. Nuclear Magnetic Resonance Spectrum of D-Mannitol (Lot No. 4644)

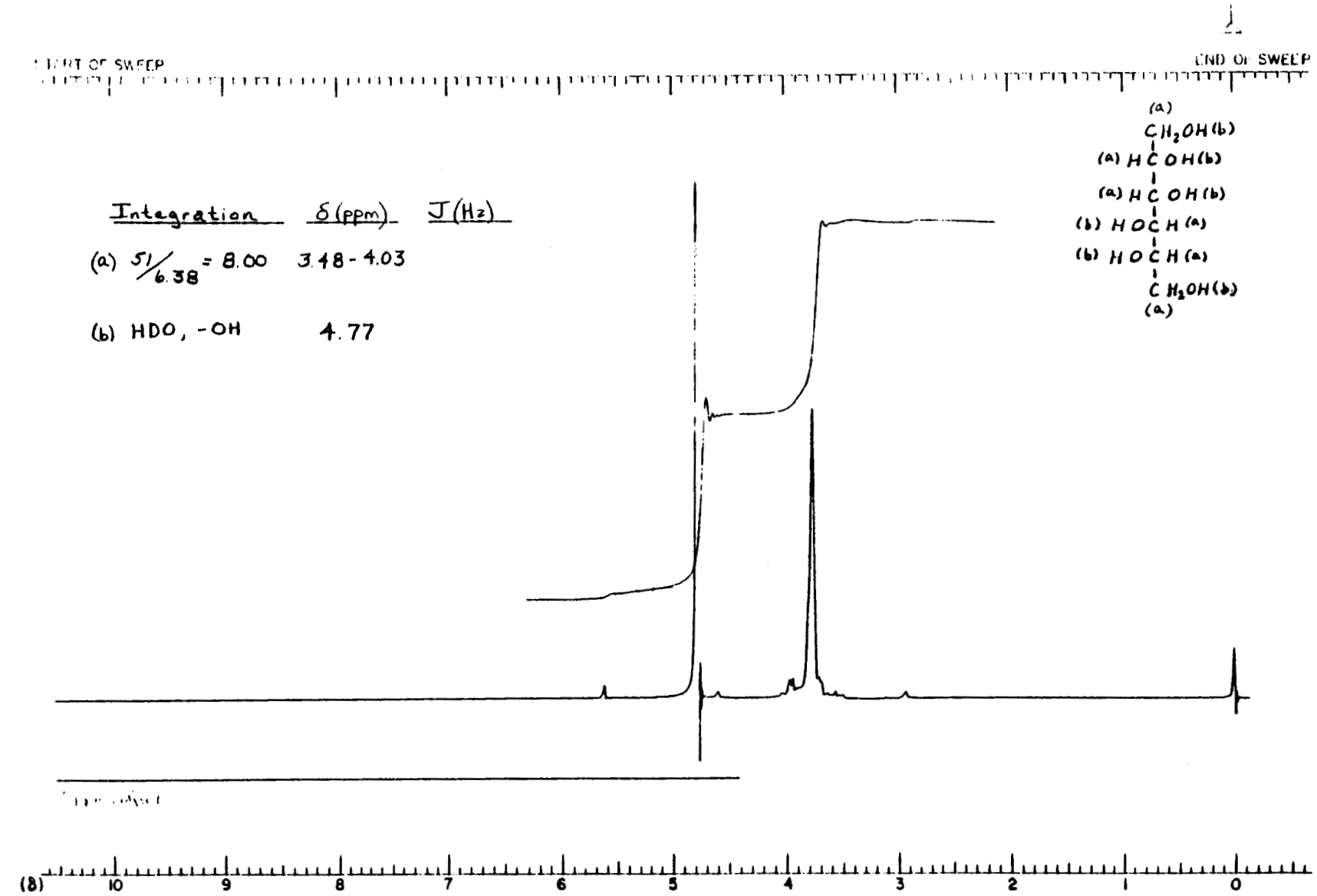

Figure 9. Nuclear Magnetic Resonance Spectrum of D-Mannitol (Lot No. 00041)

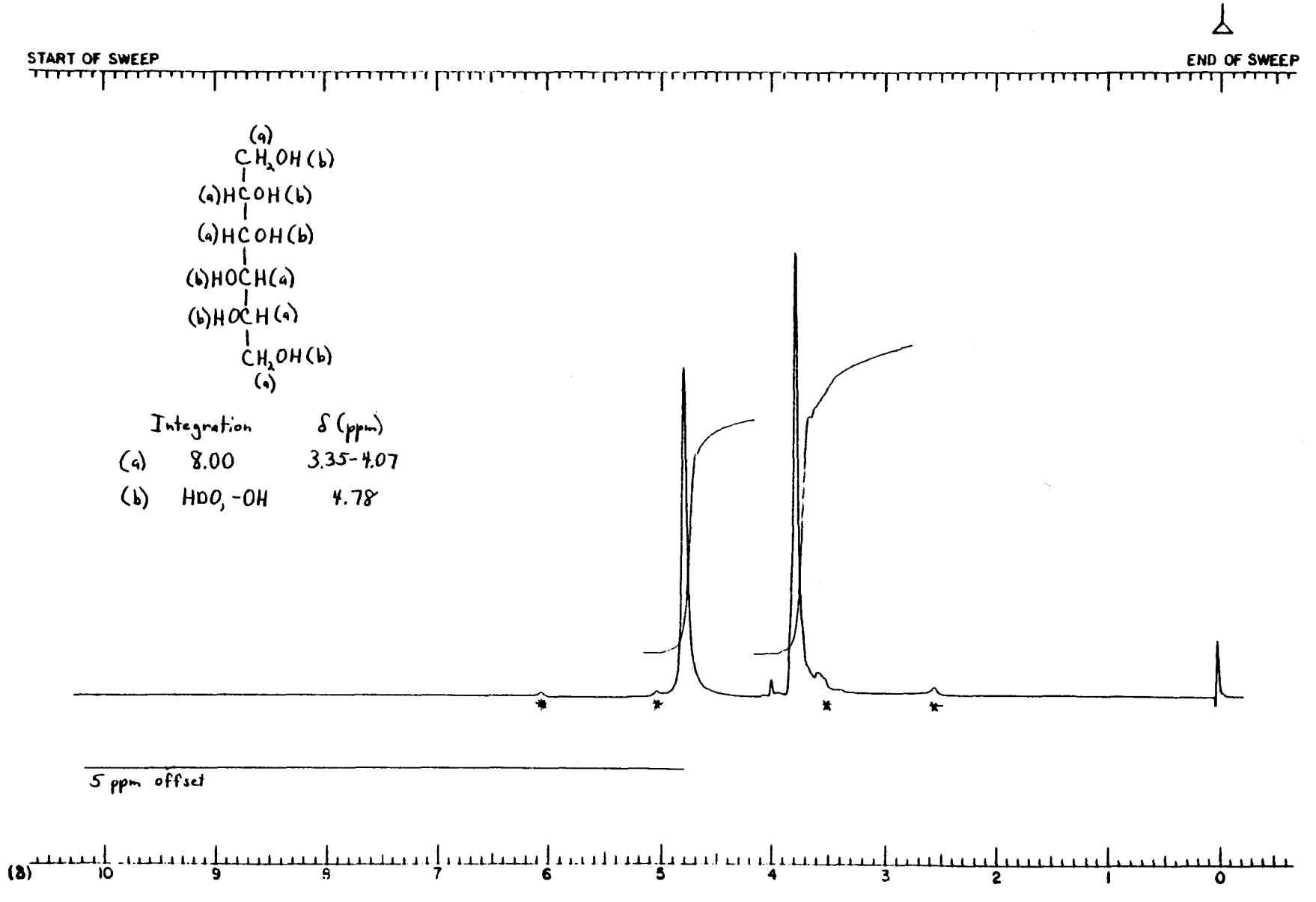

Figure 10. Nuclear Magnetic Resonance Spectrum of D-Mannitol (Lot No. 20022)

APPENDIX F

ANALYSIS FOR STABILITY OF D-MANNITOL (MIDWEST RESEARCH INSTITUTE)

APPENDIX F

A. STABILITY OF BULK CHEMICAL

Samples of D-mannitol were stored for 2 weeks at -20°, 5°, 25°, and 60°C and then analyzed by the periodate-iodate thiosulfate titration method (U.S. Pharmacopeia, 1975).

B. RESULTS

Storage Temperature (°C)	Average Percent Compound Recovered
-20	97.6 ± 0.3
5	98.1 ± 0.3
25	98.2 ± 0.3
60	97.8 ± 0.3

C. CONCLUSION

D-Mannitol is stable under conditions of storage for 2 weeks at temperatures of up to 60°C.

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR HOMOGENEITY AND STABILITY (MIDWEST RESEARCH INSTITUTE)

APPENDIX G

A. HOMOGENIZATION

1. *Mixing and sampling protocol:* D-Mannitol and Wayne Lab-Blox® meal were mixed in equal amounts (152.8 g each). Then 604.4 g of plain feed was placed in a Patterson-Kelly® shell blender, followed by the above premix, equally distributed, and finally a second 604.4-g portion of plain feed (total D-mannitol, 152.8 g; total feed, 1,361.5 g; 10.1% chemical-on-feed mixture). At elapsed mixing times of 5, 10, and 15 minutes, samples were removed from the top of each shell and the bottom trap of the blender for subsequent analysis.

2. *Extraction and analysis procedure:* Two-gram samples of the D-mannitol/feed mixtures were mixed with 50 ml of water in an ultrasonic vibratory bath for 30 seconds and then triturated for 1 minute using a Polytron® high-speed blender. The resulting mixture was centrifuged, and the aqueous supernatant was decanted into a 100-ml volumetric flask. The extraction was repeated with fresh water on the feed residue, and the centrifuged supernatant was combined with the first supernatant solution and made up to the 100-ml volume with additional water.

One-milliliter aliquots of the aqueous extract solutions were mixed with 3 ml of n-butaneboronic acid solution (in pyridine, 10 mg/ml). The resulting solution contains a 1:15 molar ratio of D-mannitol: n-butaneboronic acid; lower ratios adversely affected the yield of the mannitol boronate ester (the species detected in the vapor-phase chromatographic analysis). The derivative solutions were placed in the ultrasonic vibratory bath for 30 seconds before injection into the chromatograph.

Instrument: Tracor MT-220 Vapor-phase chromatograph

Column: 3% OV-17 on Chromosorb Q, 80/100 mesh, 1.5 m x 4 mm I.D., glass, silanized

Detector: Flame ionization

Temperature: Inlet, 250°C
Oven, 210°C, isothermal
Detector, 260°C

Retention time of derivative: 2.9 minutes

3. *Results*

Sample Time (min)	Sampling Location	Average Percent Compound Recovered *(a)*
5	Right	11.1 ± 1.1
5	Left	12.5 ± 1.1
5	Bottom	10.3 ± 1.1
10	Right	12.0 ± 1.1
10	Left	12.4 ± 1.1
10	Bottom	9.6 ± 1.1
15	Right	11.3 ± 1.1
15	Left	11.5 ± 1.1
15	Bottom	10.3 ± 1.1

(a) Corrected for spike recovery yield of 102%

4. *Conclusion:* The most homogeneous mixture is obtained after 15 minutes mixing time.

B. HEAT STABILITY

1. *Mixing and storage:* D-Mannitol (2.5094 g) and Wayne Lab-Blox® Rodent Feed (22.5022 g) were mixed in a mortar. Samples of the mixture were removed and stored for 2 weeks at -20°, 5°, 25°, and 45°C, respectively. These samples were then extracted, derivatized, and analyzed by vapor-phase chromatography.

2. *Analysis results*

Storage Temperature (°C)	Average Percent Compound Recovered *(a)*
-20	10.0 ± 1.1
5	10.5 ± 1.1
25	9.7 ± 1.1
45	9.5 ± 1.1

(a) Corrected for a spiked recovery value of 102%.

There is no significant difference between the samples stored at the various temperatures.

3. *Conclusion:* D-Mannitol mixed with feed is stable for 2 weeks at temperatures of up to 45°C.

APPENDIX H

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF D-MANNITOL (SOUTHERN RESEARCH INSTITUTE)

APPENDIX H

A 0.500 g feed sample was weighed out in a small sample test tube. Five milliliters of distilled water was mixed with the sample and then triturated for 30 seconds using a low speed on the Polytron blender. This mixture was transferred to a 15-ml centrifuge tube and centrifuged for 5 minutes. The supernatant from this was then mixed with Celite filter aid and filtered using a Millipore-suction filtration apparatus with a Whatman 42 filter. The extraction of the feed was then repeated and the filter paper washed with three l-ml portions of distilled H_2O. The aqueous filtrate was then decanted into a 25-ml volumetric flask and brought to volume with washings from the filter flask. A l-ml aliquot was taken from the filtered extract and dried using a gentle stream of nitrogen. After drying, a l-ml aliquot of n-butaneboronic acid in pyridine (10 mg/ml) was added to the sample and shaken well. The samples were analyzed after 4 hours by vapor phase chromatography under conditions specified.

Column: 3% OV-17 on Chromosorb Q, 80/100 mesh, 0.6 m x 4 mm I.D., glass, silanized

Detector: Flame ionization

Temperature: Inlet, 250°C
Oven, 210°C, isothermal
Detector, 260°C

Retention Time: 2.9 minutes

Injection Size: 1 μl

Results: See Table H1.

TABLE H1. ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF D-MANNITOL

Week Mixed	Week Used	Concentration *(a)* of D-mannitol for target concentration of	
		25,000 ppm	50,000 ppm
04/04/77	04/15/77		51,600
06/27/77	06/29/77	27,600	47,600
08/09/77	08/11/77	3,900 *(b)*	48,500
10/03/77	10/05/77	20,600	44,950
10/31/77	11/01/77	25,200	56,400
12/05/77	12/07/77	24,700	48,900
01/09/78	01/13/78	24,100	46,400
02/06/78	02/08/78	27,000	52,500
03/06/78	03/08/78	26,200	
04/03/78	04/05/78		49,200
05/01/78	05/03/78	25,150	47,200
06/05/78	06/07/78	27,600	49,900
06/26/78	06/28/78	24,500	46,600
07/24/78	07/26/78	23,400	48,700
08/21/78	08/23/78	24,500	49,800
09/18/78	09/20/78	27,800	51,300
10/16/78	10/18/78	26,500	51,700
11/13/78	11/15/78	23,600	47,200
12/11/78	12/13/78		50,200
12/14/78	12/16/78	26,450	
01/08/79	01/10/79	24,800	48,600
		24,800	
02/05/79	02/07/79	22,500	48,250
03/05/79	03/07/79	27,450	52,700
04/02/79	04/04/79	26,900	54,400
04/30/79	05/02/79	26,900	51,000
05/28/79	05/30/79	25,500	51,700
06/25/79	06/27/79	26,900	52,700
07/26/79	07/28/79	25,000	47,800
08/20/79	08/22/79		54,100
08/23/79	08/25/79	24,000	
09/17/79	09/19/79	24,400	50,100
10/15/79	10/17/79	23,600	43,900
11/12/79	11/14/79	23,400	48,300
12/10/79	12/12/79	24,400	26,700 *(c)*
01/07/80	01/09/80	25,200	53,800
02/04/80	02/06/80	24,500	51,600
03/03/80	03/05/80	26,000	49,000
03/31/80	04/02/80	27,400	54,700
Mean (ppm)		25,281	50,838
Standard Deviation		1,669	2,894
Coefficient of Variation (%)		6.6	5.8
Range (ppm)		20,600 - 27,800	43,900 - 56,400
Number of Samples		34	34

(a) The data presented are the averages of the results of duplicate analyses.
(b) Probably sampling error; not included in calculation of mean.
(c) Probably analyzed 25,000 ppm diet; not included in calculation of mean.

APPENDIX I

FEED CONSUMPTION BY RATS AND MICE RECEIVING D-MANNITOL IN THE CHRONIC STUDY

TABLE I1. FEED CONSUMPTION BY RATS RECEIVING D-MANNITOL IN THE CHRONIC STUDY

Week	Control	Low Dose		High Dose	
	Grams Feed/ Day *(a)*	Grams Feed/ Day *(a)*	Low/ Control *(b)*	Grams Feed/ Day *(a)*	High/ Control *(b)*
Males					
4	16.0	16.0	1.0	16.0	1.0
26	15.0	19.0	1.3	16.0	1.1
48	17.4	17.4	1.0	16.4	0.9
68	16.0	17.0	1.1	17.0	1.1
89	14.0	15.0	1.1	14.0	1.0
104	14.0	15.0	1.1	15.0	1.1
Mean	15.4	16.6	1.1	15.7	1.0
SD *(c)*	1.3	1.6	0.1	1.1	0.1
CV *(d)*	8.4	9.6	9.1	7.0	10.0
Females					
4	12.0	12.0	1.0	10.0	0.8
26	11.0	11.0	1.0	11.0	1.0
48	10.6	10.6	1.0	11.6	1.1
68	12.0	11.0	0.9	11.0	0.9
89	11.0	11.0	1.0	11.0	1.0
104	12.0	12.0	1.0	11.0	0.9
Mean	11.4	11.3	1.0	10.9	1.0
SD *(c)*	0.6	0.6	0.0	0.5	0.1
CV *(d)*	5.3	5.3	0.0	4.6	10.0

(a) Grams of feed consumed per animal per day.
(b) Grams of feed consumed per day by the dosed group divided by that for the controls.
(c) Standard deviation
(d) Coefficient of variation ¤ (standard deviation/mean) x 100

TABLE I2. FEED CONSUMPTION BY MICE RECEIVING D-MANNITOL IN THE CHRONIC STUDY

	Control	Low Dose		High Dose	
Week	Grams Feed/ Day *(a)*	Grams Feed/ Day *(a)*	Low/ Control *(b)*	Grams Feed/ Day *(a)*	High/ Control *(b)*
Males					
5	10.3	10.3	1.0	10.3	1.0
27	8.0	8.0	1.0	9.0	1.1
48	9.3	9.3	1.0	9.3	1.0
69	9.3	9.3	1.0	9.4	1.0
87	6.0	6.0	1.0	5.0	0.8
104	5.8	5.8	1.0	4.8	0.8
Mean	8.1	8.1	1.0	8.0	1.0
SD *(c)*	1.9	1.9	0.0	2.4	0.1
CV *(d)*	23.5	23.5	0.0	30.0	10.0
Females					
5	10.3	10.3	1.0	10.3	1.0
27	9.0	9.0	1.0	9.0	1.0
48	9.3	8.2	0.9	8.2	0.9
69	9.4	8.3	0.9	9.3	1.0
87	6.0	6.0	1.0	6.0	1.0
104	5.8	5.8	1.0	5.8	1.0
Mean	8.3	7.9	1.0	8.1	1.0
SD *(c)*	1.9	1.7	0.1	1.8	0.0
CV *(d)*	22.9	21.5	10.0	22.2	0.0

(a) Grams of feed consumed per animal per day.
(b) Grams of feed consumed per day by the dosed group divided by that for the controls.
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) x 100

APPENDIX J

HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN UNTREATED CONTROL FEMALE B6C3F1/N MICE

TABLE J1. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN UNTREATED CONTROL FEMALE B6C3F1/N MICE *(a)*

Laboratory	Lymphocytic Leukemia	All Leukemias	Lymphoma or Leukemia
Battelle	7/350 (2.0%)	8/350 (2.3%)	85/350 (24.3%)
Dow	2/99 (2.0%)	3/99 (3.0%)	41/99 (41.4%)
Frederick	1/435 (0.2%)	5/435 (1.1%)	100/435 (23.5%)
Hazleton	0/100 (0.0%)	1/100 (1.0%)	26/100 (26.0%)
Litton	4/513 (0.8%)	17/513 (3.3%)	133/513 (25.9%)
Mason	5/817 (0.6%)	7/817 (0.9%)	248/817 (30.4%)
Southern	8/505 (1.6%)	10/505 (2.0%)	96/505 (19.0%)
Total	27/2819 (1.0%)	51/2819 (1.8%)	729/2819 (25.9%)
High	5/50 (10%)	5/50 (10%)	31/50 (62%)
Low	0/50 (0%)	0/50 (0%)	4/50 (8%)

(a) Data as of January 17, 1981. Range is presented for groups of 35 or more animals.

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