NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 248

CARCINOGENESIS STUDIES OF 4,4-METHYLENEDIANILINE DIHYDROCHLORIDE (CAS NO. 13552-44-8) IN F344/N RATS AND B6C3F$_1$ MICE (DRINKING WATER STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of 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 STUDIES
OF
4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

(CAS NO. 13552-44-8)

IN F344/N RATS AND B6C3F$_1$ MICE
(DRINKING WATER STUDIES)

NATIONAL TOXICOLOGY PROGRAM
Box 12233
Research Triangle Park
North Carolina 27709

June 1983

NTP-81-143
NIH Publication No. 83-2504
NTP TR 248

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

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 has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

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.

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).

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room 835B, Westwood Towers, 5401 Westbard Ave., 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.

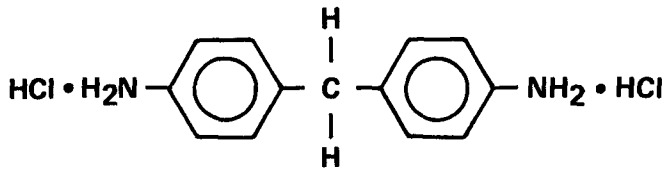
TABLE OF CONTENTS

TABLES

FIGURES

APPENDIXES

CARCINOGENESIS STUDIES OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE



4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

CAS NO. 13552-44-8
$C_{13}H_{14}N_2$ Mol. Wt. 198.27

ABSTRACT

Carcinogenesis studies of 4,4'-methylenedianiline dihydrochloride (98.6% pure) were conducted by administering this chemical in the drinking water of F344/N rats and $B6C3F_1$ mice. Groups of 50 rats and 50 mice of each sex received drinking water containing 150 or 300 ppm 4,4'-methylenedianiline dihydrochloride (dosage expressed as the free base) for 103 weeks. Groups of 50 rats and 50 mice of each sex, given drinking water adjusted with 0.1N HCl to the pH (3.7) of the 300-ppm formulation, served as controls.

Survival was comparable among groups except for male mice receiving the high dose of 4,4'-methylenedianiline dihydrochloride; survival in that group was lower (P=0.006) than that in controls. Mean body weight was reduced in high dose female rats and in high dose male and female mice. Water consumption was reduced in a dose-related manner in both sexes of rats. No compound-related clinical effects were observed.

Compound-related nonneoplastic lesions of the thyroid in female rats included follicular cysts and hyperplasia. The incidence of thyroid follicular cell hyperplasia was elevated in high dose male and female mice. The incidences of thyroid neoplasms in the high dose groups were elevated compared with those of control groups for both sexes of both species. Thyroid follicular cell carcinoma was increased in male rats (controls, 0/49; low dose, 0/47; high dose, 7/48, 15%; $P \leq 0.012$). Follicular cell adenoma was increased in high dose female rats (0/47; 2/47, 4%; 17/48, 35%: $P < 0.001$), in high dose male mice (0/47; 3/49, 6%; 16/49, 33%: $P < 0.001$), and in high dose female mice (0/50; 1/47, 2%; 13/50, 26%: $P < 0.001$) as compared with controls. In female rats, thyroid C-cell adenoma was also elevated in a dose-related manner (0/47; 3/47, 6%; 6/48, 13%, $P \leq 0.029$).

Dose-related increases in nonneoplastic lesions were observed for male rats (nonspecific liver dilatation) and for male and female rats (fatty metamorphosis and focal cellular change). Liver degeneration was present in 80% of the low dose and 60% of the high dose male mice but was not found in controls. Neoplastic nodules of the liver were observed at greater incidences ($P \leq 0.002$) for low and high dose male rats as compared with controls (control, 1/50, 2%; low dose, 12/50, 24%, $P \leq 0.002$; high dose, 25/50, 50%, $P < 0.001$). Hepatocellular adenoma was increased in a dose-related manner in dosed female mice (3/50, 6%; 9/50, 18%; 12/50, 24%, $P < 0.011$). Hepatocellular carcinoma was observed in greater incidence in dosed male mice (10/49, 20%; 33/50, 66%, $P < 0.001$; 29/50, 58%, $P < 0.001$) and in high dose female mice (1/50, 2%; 6/50, 12%; 11/50, 22%, P=0.002).

Male rats had a dose-related increase in kidney mineralization. Nephropathy was increased in dosed mice of both sexes; renal papillary mineralization was greater in high dose male and female mice than in the controls.

Other tumors that were elevated in dosed animals included adrenal pheochromocytomas in male mice (control, 2/48, 4%; low dose, 12/49, 24%, $P \leq 0.006$; high dose, 14/49, 29%; $P \leq 0.001$), alveolar/bronchiolar adenoma in female mice (1/50, 2%; 2/50, 4%; 6/49, 12%, $P \leq 0.05$) and malignant lymphomas in female mice (13/50, 26%; 28/50, 56%, P=0.002; 29/50, 58%; P=0.001).

Uncommon tumors were observed in dosed animals at low incidences but may be important because the historical control incidences are very low: bile duct adenoma in 1/50 high dose male rats (historical control, 0/3,633), transitional-cell papillomas of the urinary bladder in female rats (historical control, 3/3,644, 0.08%; low dose, 2/50, 4%; high dose, 1/50, 2%) and granulosa cell tumors of the ovary in female rats (historical control, 11/3,642, 0.3%; low dose, 3/50, 6%; high dose, 2/50, 4%).

Decreases in tumor incidence were observed for leukemia in male rats (control, 12/50, 24%; low dose, 6/50, 12%; high dose, 5/50, 10%, P=0.048) and alveolar or bronchiolar adenomas (combined) in male mice (12/49, 24%; 9/49, 18%; 3/49, 6%, $P \leq 0.011$).

Under the conditions of these studies, 4,4′-methylenedianiline dihydrochloride was carcinogenic for F344/N rats and $B6C3F_1$ mice of each sex, causing significantly increased incidences of thyroid follicular cell carcinomas in male rats, thyroid follicular cell adenomas in female rats and in mice of each sex, C-cell adenomas of the thyroid gland in female rats, neoplastic nodules in the liver of male rats, hepatocellular carcinomas in mice of each sex, adenomas of the liver and malignant lymphomas in female mice, and adrenal pheochromocytomas in male mice.

CONTRIBUTORS

These carcinogenesis studies of methylenedianiline dihydrochloride were conducted at Mason Research Institute under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The 2-year study was begun in August 1978 and completed in September 1980.

Principal Contributors at Mason Research Institute
57 Union Street
Worchester, Massachusetts 01608
(Conducted bioassay and evaluated tissues)

A. Block, Ph.D.
Assistant Principal Investigator

A. Good, M.A.
Technical Coordinator

R.S. Grant, M.A.
Operations Coordinator

M. Hagopian, Ph.D.
Chemist

H. Lilja, Ph.D.
Principal Investigator

R. Monson, M.A.
Bioassay Coordinator

A.S.K. Murthy, Ph.D.
Pathologist

G. Wade, B.S.
Bioassay Coordinator

E. Zepp, M.A.
Operations Coordinator

Principal Contributors at Tracor Jitco
1776 East Jefferson Street
Rockville, Maryland 20852
(Prepared preliminary summary report)

E. Cremmins, M.A.
Technical Editor

C. E. Dean, B.S.
Production Editor

A. Jacobs, Ph.D.
Bioscience Writer

J. Keller, Ph.D.
Director, Bioassay Program

M. Levy, M.A.
Technical Editor

S. Olin, Ph.D.
Program Associate Director

M. Stedham, D.V.M.
Pathologist

L. Scheer, B.S.
Production Editor

W. Theriault, Ph.D.
Manager, Technical Reports

J. Tomaszewski, Ph.D.
Chemist

J. Warner, M.S.
Statistician

Principal Contributors at the National Toxicology Program
National Institute of Environmental Health Sciences
Box 12233
Research Triangle Park
North Carolina 27709
(Evaluated the experiment, interpreted the
results, and reported the findings)

James C. Lamb, Ph.D. (Chemical Manager)
Gary A. Boorman, D.V.M., Ph.D
Rajendra S. Chhabra, Ph.D.
Michael P. Dieter, Ph.D.
J. Fielding Douglas, Ph.D.
Charles K. Grieshaber, Ph.D.
Larry Hart, Ph.D.
Joseph Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
Ernest E. McConnell, D.V.M.
John A. Moore, D.V.M.
Raymond Tennant, Ph.D.

The pathology report and selected slides from the carcinogenesis studies of 4,4'-methylenedianiline dihydrochloride were evaluated on 15 July 1981 by the NTP Pathology Working Group composed of:

Dr. G. Boorman
Dr. R. Maronpot
Dr. E. McConnell
Dr. K. Ayers (Burroughs-Wellcome)
Dr. R. Kovatch (Tracor Jitco)

REVIEWERS

National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee

Margaret Hitchcock, Ph.D. (Chairperson)
Pharmacology, Toxicology
John B. Pierce Founcation Laboratory
New Haven, Connecticut

Curtis Harper, Ph.D.
Associate Professor of Pharmacology
University of North Carolina
Chapel Hill, North Carolina

Alice Whittemore, Ph.D.*
Biostatistics
Stanford University School of Medicine
Palo Alto, California

Ad Hoc Subcommittee Panel of Experts

Norman Breslow, Ph.D.
Biostatistics
University of Washington
Seattle, Washington

Robert M. Elashoff, Ph.D.
Biostatistics
University of California
at Los Angeles
Jonsson Comprehensive Cancer Center
Los Angeles, California

Joseph Highland, Ph.D.
Toxicology
Environmental Defense Fund
Washington, D.C.

J. Michael Holland, Ph.D., D.V.M.
Pathology
Department of Biology
Oak Ridge National Laboratory
Oak Ridge, Tennessee

Frank Mirer, Ph.D. (Principal Reviewer)
Toxicology
International Union,
United Auto Workers
Detroit, Michigan

Robert A. Scala, Ph.D. (Principal Reviewer)
Exxon Corporation
East Millstone, New Jersey

Bernard Schwetz, Ph.D., D.V.M.
Toxicology Research Laboratory
Dow Chemical U.S.A.
Midland, Michigan

James Swenberg, Ph.D., D.V.M.
Chief of Pathology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Stan D. Vesselinovitch, D.V.Sc.*
Departments of Radiology and Pathology
University of Chicago
Chicago, Illinois

Mary Vore, Ph.D. (Principal Reviewer)
Pharmacology
University of Kentucky
College of Medicine
Lexington, Kentucky

*Unable to attend June 16, 1982 meeting

SUMMARY OF PEER REVIEW COMMENTS ON THE CARCINOGENESIS STUDIES OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

On 16 June 1982 this carcinogenesis studies technical report on 4,4'-methylenedianiline dihydrochloride underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. This public review meeting began at 9:00 a.m. in the Conference Center, building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The following precis represents the critiques made by the principal reviewers, as well as comments from and discussion by the Peer Review Panel, NTP staff, and attendees.

Dr. Scala, as a principal reviewer for the report of the carcinogenesis studies of 4,4'-methylenedianiline dihydrochloride (MDA), said the conclusions were supported by the data and statistical analyses as presented. Dr. Scala said the doses used (150 and 300 ppm MDA) may have been too high; 100 and 200 ppm may have been more appropriate. He had several comments relating to the possible impact of water deprivation, room temperature, and relative humidity excursions on the results obtained. He specifically called for a balanced discussion of mechanisms to include the possibility of hepatocarcinogenic activity being secondary to reported hepatotoxicity and being via a non-genetic mechanism, but noted that in all other areas the report did present a balanced viewpoint. Discussion on the points in Dr. Scala's comments has been incorporated.

As a second principal reviewer, Dr. Vore agreed with the conclusions. She said that dose-related increases in a number of nonneoplastic lesions of the liver and kidneys should be included in the discussion section. She said the kidney, like the liver, possesses enzymes which could convert MDA to proposed reactive intermediates which may, in turn, be responsible for the renal toxicity; she felt that mention of this would enhance the discussion. She thought the statement that MDA has a special affinity for the thyroid hormone receptor was highly speculative and should be modified [comments on these points were added]. There was discussion concerning the inclusion of general scientific speculations in this and other reports, and it was agreed that some speculation was appropriate and should be encouraged.

As a third principal reviewer, Dr. Mirer agreed with the conclusions. He noted that the decrease in hematopoietic tumors in male rats is similar to observations in tests of other amine and dye compounds in the bioassay program, and said the association between the decrease in hematopoietic tumors and an increase in tumors at other sites should be explored. Dr. J. Haseman, NTP, said that in a review of 25 to 30 of the most recent bioassays, particularly feeding studies, there does seem to be a recurring association of increased liver tumor incidence with concurrent decreases in hematopoietic tumors.* Dr. Holland cautioned against trying to draw too general a biological significance from this analysis.

Dr. Holland discussed the effects of water deprivation and water pH on the health and survival of animals, especially mice, and indicated he did not believe either was a problem with the MDA study. There was discussion concerning inclusion of information on apparent "genetic drift" of the animals in some reports but not others. This resulted because the "drift" or contamination did not occur in animals in some laboratories; the possible alternation was not present. For these, it was agreed that where there was a lack of contamination that fact should be stated in the report.

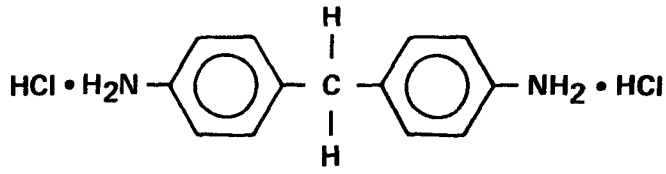
Dr. Scala moved that the report on the bioassay of 4,4'-methylenedianiline dihydrochloride be accepted with the modifications as discussed. Dr. Mirer seconded the motion and the technical report was approved unanimously by the Peer Review Panel.

---

*See Haseman, J.K.; Patterns of tumor incidence in two-year cancer bioassay feeding studies in Fischer 344 rats. Fund. Appl. Toxicol. 3:1-9; 1983.

I. INTRODUCTION

I. INTRODUCTION



4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

CAS NO. 13552-44-8
$C_{13}H_{14}N_2$ Mol. Wt. 198.27

4,4'-Methylenedianiline (CAS No. 101-77-9) is used primarily as a chemical intermediate in the closed system production of isocyanates and polyisocyanates. These chemicals are used extensively in the manufacture of rigid polyurethane foams for thermal insulation and in the production of semiflexible polyurethane foams for automobile safety cushioning (NIOSH, 1976). The saturated isocyanate of 4,4'-methylenedianiline—4,4'-methylene-bis(cyclohexylisocyanate)—is an intermediate in the production of light-stable, high-performance polyurethane coatings (IARC, 1974b). 4,4'-Methylenedianiline is also a curing agent for epoxy resins and urethane elastomers, a dye intermediate, and a corrosion inhibitor (IARC, 1974a; Kirk-Othmer, 1965; Merck, 1976).

4,4'-Methylenedianiline has been identified in aqueous extracts of autoclaved material developed for medical use (Darby et al., 1978). It has been approved by the U.S. Food and Drug Administration as a catalyst or cross-linking agent in epoxy resins that coat containers for beverages having an alcohol content of up to 8% (USCFR, 1977). According to production data, about 352 to 396 million pounds of 4,4'-methylenedianiline are produced annually in the United States; only 10% of the 4,4'-methylenedianiline is purified and the remaining 90% is used in captive systems for the production of polyisocyanates (Personal Communication from EPA, June 23, 1982).

The oral LD_{50} value of 4,4'-methylenedianiline is 830 mg/kg body weight in Wistar rats (Pludro et al., 1969). 4,4'-Methylenedianiline has produced toxic effects on the liver, spleen, and bile duct when administered to rats by gavage or in feed. Atrophy of liver parenchyma was observed in Wistar rats given 83 mg/kg/day for 12 weeks (Pludro et al., 1969); cirrhosis was found in 7/7 male rats administered an average dose of 38 mg/kg, 5 days per week, for 17 weeks (Munn, 1967); necrosis of the proximal convoluted tubules has been associated with compound administration; and hemangiomas were found in the liver of 2/30 albino rats administered 20 mg/kg by gavage for 16 weeks (Golke, 1978).

Increased relative spleen weights were observed in Wistar rats given 83 mg/kg/day for 12 weeks (Pludro et al., 1969); and nonneoplastic lesions of the spleen have been associated with administration of 4,4'-methylenedianiline (Calder et al., 1973). Bile duct proliferation has been found in male rats fed diets containing 1,000 ppm 4,4'-methylenedianiline for 40 weeks (Fukushima et al., 1979) and in albino rats administered 20 mg/kg/day for 16 weeks (Golke, 1978). Adrenal, uterine, and thyroid hypertrophy were observed in castrated female Sprague Dawley rats given daily 150 mg/kg doses of 4,4'-methylenedianiline by gavage for 14 days. Thyroid weights nearly doubled during the dosing period (Tullner, 1960).

I. INTRODUCTION

Nonneoplastic toxic effects have been attributed to ingestion of 4,4'-methylenedianiline by humans. The inadvertent contamination of flour with 4,4'-methylenedianiline and the subsequent ingestion of bread made with that flour led to an episode of human poisoning by 4,4'-methylenedianiline (Kopelman et al., 1966). The compound proved to be hepatotoxic to humans, but all 84 affected persons recovered without incident. Occupational exposure to 4,4'-methylenedianiline caused a similar toxic hepatitis and eventually led to the containment of the manufacturing process using 4,4'-methylenedianiline (McGill and Motto, 1974).

4,4'-Methylenedianiline is mutagenic for *Salmonella typhimurium* TA100 and TA98 only after metabolic activation (Takemura and Shimizu 1978; Darby et al., 1978; Lavoie et al., 1979; Shimizu and Takemura, 1976).

Animal data on the carcinogenicity of 4,4'-methylenedianiline have been judged insufficient (IARC, 1974a). When 4,4'-methylenedianiline was administered by gavage in arachis oil to 24 male rats (strain not specified), 5 days per week for 17 weeks, at a total dose of 3.3 g/kg, a hepatoma was found in one animal killed after 26 months on study and in a second animal killed after 32 months (Munn, 1967). In male rats administered 6.0 g/kg by gavage (the total 18-month dose), 1/24 had a liver tumor after 1 year and a second animal had a liver tumor after 2 years on study. In a concurrent study, 18/24 rats had malignant liver tumors and 2/24 had benign tumors when administered the analog 3,3'-dimethyl-4,4'-diaminodiphenylmethane in arachis oil by gavage for 18 months (a total dose of 10.2 g/kg). Control data were not published for either study.

A total of 29 benign tumors, 33 malignant tumors, and 4 hepatomas were reported among 25 male and 25 female Wistar rats subcutaneously administered methylenedianiline at doses of 30 to 50 mg/kg for 1- to 3-week intervals over 100 weeks; a total of 15 benign and 16 malignant tumors were reported among the 25 male and 25 female controls (Steinhoff and Grundmann, 1970).

Rubino et al. (1982) reported epidemiological evidence that associates 4,4'-methylene bis(2-methylaniline)—the 2,2'-dimethyl analog of 4,4'methylenedianiline—and *o*-toluidine with an increase in mortality from urinary bladder cancer in dyestuff factory workers in Northern Italy. These authors stress "that precursors of fuchsin and safranine T (namely, *o*-toluidine or 4,4'-methylene bis(2-methylaniline)) should be considered causal agents of bladder cancer both during manufacture and use...."

4,4'-Methylenedianiline dihydrochloride was tested because of its structural relationship to known carcinogens (e.g., benzidine, IARC, 1982) and because previous bioassays of 4,4'-methylenedianiline were not considered to be adequate. Since 4,4'-methylenedianiline is not stable in feed or water and the dihydrochloride salt is not stable in feed, 4,4'-methylenedianiline was tested as the dihydrochloride salt (CAS No. 13552-44-8) in drinking water.

II. MATERIALS AND METHODS

CHEMICAL ANALYSES

DRINKING WATER FORMULATIONS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDY

Study Design

Source and Specifications of Test Animals

Animal Maintenance

Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSES

4,4'-Methylenedianiline dihydrochloride was obtained in two lots from Eastman Kodak Company (Rochester, NY). Lot No. A6A was used for the 14-day and 13-week studies and Lot No. A8 was used for the entire 2-year study.

Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO). Results of elemental analyses of Lot No. A6A agreed with the theoretical values; for Lot No. A8, results for carbon and nitrogen were low, while those for hydrogen and chlorine agreed with theoretical values (Appendix G). Non-aqueous titration of the amine groups indicated that Lot No. A6A was 102% pure and Lot No. A8 was 98.6% pure.

A single impurity was found at the origin in Lot No. A6A by thin-layer chromatography, whereas three impurities were detected in Lot No. A8 in the same systems. Vapor-phase chromatography of the same lot samples identified four impurities with cumulative areas less than 0.5% of the major peak in Lot No. A6A, and two impurities with areas 1% and 0.25% of the major peak, respectively, in Lot No. A8. The infrared, ultraviolet, and nuclear magnetic resonance spectra were consistent with those expected for the structure and with literature spectra.

The chemical was stored in the cold at the bioassay laboratory throughout the study, and periodic reanalysis by infrared and gas-liquid chromatography indicated no significant change in composition during that time period.

DRINKING WATER FORMULATIONS

A tissue homogenizer was used to dissolve methylenedianiline dihydrochloride in an aliquot of tap water. Then the solution was added to the appropriate amount of tap water and stirred. The dosage preparations were made and stored in acetone-rinsed, dose-specific Nalgene® carboys. Carboys were stored in the dark at 0°±5°C.

4,4'-Methylenedianiline dihydrochloride (1,000 and 10,000 ppm in water) was found to be stable for 7 days at room temperature (Appendix H). Samples of formulated drinking water were periodically analyzed at Mason Research Institute. The results of these analyses and of referee analyses at Midwest Research Institute indicated that the samples analyzed were properly formulated (Appendix I).

FOURTEEN-DAY STUDIES*

Male and female F344/N rats and B6C3F1 mice were obtained from Harlan Industries and held for approximately 6 weeks (rats) or 4 weeks (mice) before the study began (Table 1). Rats were 10 weeks old and mice were 8 weeks old when placed on study.

Groups of five males and five females of each species were administered drinking water containing 0, 200, 400, 800, 1,600, or 3,200 ppm 4,4'-methylenedianiline (prepared from the dihydrochloride but expressed as the free base) for 14 days; all groups received untreated water on day 15. The pH of the water given to controls was adjusted with 0.1N HCl to within 0.02 pH units of the water containing 3,200 ppm of the test substance.

Rats were housed individually and mice were housed five per cage. All animals received feed and dosed or untreated water *ad libitum*. Details of animal maintenance are presented in Table 1. Rats and mice were observed twice daily for mortality, and the initial and final weights for each animal were recorded. Necropsies were performed on all animals.

*There was no single-dose study with 4,4'-methylenedianiline dihydrochloride.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxicity of 4,4'-methylenedianiline dihydrochloride and to determine the concentration to be used in the chronic studies.

Four-week-old male and female F344/N rats and five-week-old B6C3F$_1$ mice were obtained from Harlan Industries, observed for 3 weeks, and then randomized by weight and assigned to test groups so that average cage weights were approximately equal for all animals of the same sex and species.

Rats and mice were housed five per cage in polycarbonate cages covered with nonwoven polyester filter sheets (Table 1). Racks and filters were replaced once every 2 weeks. Cages and bedding were replaced twice per week and water bottles were replaced three times per week.

Drinking water containing 0, 25 (mice), 50, 100, 200, 400, or 800 (rats) ppm 4,4'-methylenedianiline (prepared from the dihydrochloride but expressed as the free base) was offered for 13 weeks to groups of 10 males and 10 females of each species. Formulated water was prepared from tap water and the required amount of 4,4'-methylenedianiline dihydrochloride (Lot No. A6A). The pH of the water for the controls was adjusted to that of the water containing 800 ppm by adding 0.1N HCl.

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

At the end of the 91-day study, survivors were killed. Necropsies were performed on all animals. The following specimens were examined histopathologically for control and high-dose groups: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord. The liver, pituitary, and thyroid of rats receiving 400 ppm and the liver and thyroid of rats receiving 200 ppm were examined histopathologically, since microscopic lesions were noted in those tissues at higher dose levels. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats and 50 mice of each sex were given free access to drinking water containing 150 or 300 ppm 4,4'-methylenedianiline dihydrochloride for 103 weeks. Concurrent control groups of 50 rats and 50 mice of each sex received drinking water adjusted with 0.1 N HCl to the pH of the 300-ppm formulation. The average pH was 3.7; for the 300 ppm concentration, 59 pH determinations were made: mean = 3.73, S.D. = 0.32, range = 3.22-4.78.

Source and Specifications of Test Animals

Four-week-old F344/N rats and 9-week-old B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 14 days (rats) or 19 days (mice) and then assigned to cages according to a table of random numbers. The cages were then assigned to control and dosed groups according to another table of random numbers.

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of inbred mice used to produce the hybrid B6C3F$_1$ test animal. In mid-1981, data were obtained that showed incompatibility between th NIH C3H reference colony and the C3H colony from a Bioassay Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic homogeneity via isozyme and protein electrophoregrams which demonstrate phenotype expressions of known genetic loci.

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of random bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic non-uniformity in the hybrid mice on the study results is not known. However, the studies are valid, since matched concurrent controls were included.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages covered with nonwoven polyester filter sheets (Table 1). Racks and filters were changed once every 2 weeks. Cages, bedding, and glass water bottles were replaced twice per week. Diets were available *ad libitum.*

The temperature in the animal room was analyzed for the period from January 2, 1978 to February 13, 1980, except for the period between April 16, 1978 and August 9, 1978 when no data were available. The data comprised once daily readings, usually taken in the morning, for the period January 2, 1978 to October 28, 1979 and twice daily readings taken in the morning and afternoon between October 29, 1979 and February 13, 1980. A total of 729 temperature readings were recorded, of which 725 (99.5%) were in the range 68°F to 79°F. The highest reading (80°F) was observed on January 28, February 15, March 8, and April 5, 1978. The lowest reading (68°F) was observed on September 10 and 12, 1979. Humidity was uncontrolled (range, 8% to 78%, average 41%). Humidity measurements (once daily) indicated that of 607 readings 5 (0.8%) were greater than 60%, 144 (18.8%) were in the range of 40% to 59%, 101 (16.6%) were 30% to 39%, 142 (23.1%) were 20% to 29%, 199 (32.8%) were 10% to 19%, 33 (5.4%) were 6% to 9%, and 13 (2.1%) were 0% to 5%. Ten to twelve changes of room air per hour were provided. Fluorescent lighting provided illumination 12 hours per day.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of morbidity or mortality. Clinical signs were recorded monthly. Body weights by cage were recorded every week for the first 13 weeks and monthly thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. The average water consumption per animal was calculated by dividing the total water 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.

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

Necropsies were performed on all animals found dead and on those killed at the end of the study, unless precluded in whole or in part by autolysis or cannibalization. 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 Maronpot and Boorman (in press). The classification of neoplastic nodules was done 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. All reported P-values for the survival analyses are two-sided.

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

For studies in which there is little effect of compound administration on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pair-wise 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 numbers of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel 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 the following 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 comparisions and the Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart et al., 1979). These tests were based on the overall proportion of tumor-bearing animals. All reported P values for the analyses of tumor incidences are one-sided.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS

	14-Day Studies	13-Week Studies	2-Year Studies
Experimental Design			
Size of Test Groups	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	0, 200, 400, 800, 1,600, or 3,200 ppm 4,4'-methylenedianiline dihydrochloride in tap water	Rats: 0, 50, 100, 200, 400, or 800 ppm 4,4'-methylenedianiline dihydrochloride in tap water Mice: 0, 25, 50, 100, 200 or 400 ppm 4,4'-methylenedianiline dihydrochloride in tap water	0, 150, or 300 ppm 4,4'-methylenedianiline dihydrochloride in tap water, available *ad libitum;* drinking water of controls adjusted to pH of 300-ppm formulation
Duration of Dosing	14 days	13 weeks	103 weeks
Type and Frequency of Observation	Observed twice daily for 15 days	Observed twice daily for morbidity and mortality	Observed twice daily for morbidity and mortality
Necropsy and Histopathological Examination	Necropsy performed on all animals	Necropsy performed on all animals. All animals receiving tap water or highest dose examined histologically. Liver, pituitary, and thyroid of rats receiving 400 ppm, and liver and thyroid of rats receiving 200 ppm were also examined histologically	Necropsy and histopathologic examination performed on all animals
Animals and Animal Maintenance			
Species	F344/N rats; B6C3F1 mice	F344/N rats; B6C3F1 mice	F344/N rats; B6C3F1 mice
Animal Source	Harlan Industries (Indianapolis, IN)	Same as 14-day study	Charles River Breeding Laboratories (Portage, MI)
Time Held Before Start of Test	Rats: 6 weeks Mice: 4 weeks	3 weeks	Rats: 14 days Mice: 19 days
Age When Placed on Study	Rats: 10 weeks Mice: 8 weeks	Rats: 7 weeks Mice: 8 weeks	Rats: 6 weeks Mice: 12 weeks
Age When Killed	Rats: 12 weeks Mice: 10 weeks	Rats: 20 weeks Mice: 21 weeks	Rats: 111-112 weeks Mice: 116-117 weeks

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

	14-Day Studies	13-Week Studies	2-Year Studies
Method of Animal Distribution	Culled extreme weights such that all cage weights were approximately equal	Distributed by weight so that average body weights for each group were approximately equal	Assigned to cages according to a table of random numbers Cages assigned to dosed and control groups according to another table of random numbers
Feed	Wayne Lab Blox® Allied Mills, Inc	Same as 14-day study	Same as 14-day study
Water	Formulated water Available *ad libitum*, bottles replaced twice a week	Formulated water Available *ad libitum*, bottles replaced three times a week for the 13 weeks	Formulated water Available *ad libitum*, bottles replaced twice a week
Cages	Suspended galvanized steel wire mesh	Polycarbonate Lab Products, Inc , (Rochelle Park, NJ) Cages changed twice per week	Same as 13-week study
Bedding		Aspen bed® American Excelsior Co (Baltimore, MD) Changed twice per week	Same as 13-week study
Animals per Cage	Rats one Mice five	Five	Five
Cage Filters	Non-woven fiber filter bonnets	Non-woven fiber filter (Webrex), filters changed biweekly	Enviro-guard See-Through II Polyester Lab Products, Inc (Rochelle Park, NJ)
Animal Room Environment	Fluorescent lighting 12 hours per day, room air changed 10 times per hour	21 7°-28 9°C, 3%-40% relative humidity, fluorescent lighting 12 hours per day, room air changed 6-7 times per hour	16 1°-31 1°C, 8%-78% relative humidity; fluorescent lighting 12 hours per day, room air changed 10-12 times per hour
Other Chemicals on Test in Same Room	None	None	None
Chemical/Vehicle Mixture			
Preparation	Water formulated by dissolving aliquots of 4,4'-methylenedianiline hydrochloride in small amounts of tap water using a hand homogenizer prior to addition of the balance of the water	Water formulated by dissolving aliquots of 4,4'-methylenedianiline hydrochloride in small amounts of tap water using a hand homogenizer prior to addition of the balance of the water	Water formulated by first combining weighed chemical and tap water in a tissue homogenizer Chemical/water premix was then added to sufficient tap water and was stirred thoroughly
Maximum Storage Time	One week	One week	One week
Storage Conditions	Stored at 4°C	Stored in the dark at 4°C	Stored in the dark at 0° ± 5°C

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

FOURTEEN-DAY STUDIES

All animals survived to the end of the test period. All males that received 1,600 or 3,200 ppm and all females that received 800, 1,600, or 3,200 ppm lost weight (Table 2). Mean body weight gain when compared with controls was depressed in all groups, in a dose-related fashion.

Raised, crater-like foci with black contents were noted in the cardiac portion of the stomach in 3/5 males and 3/5 females that received 3,200 ppm and in 3/5 females that received 1,600 ppm. Orange discoloration was observed in the urogenital area of 3/5 females receiving 3,200 ppm and 1/5 receiving 1,600 ppm.

Water consumption relative to controls was depressed in a generally dose-related manner for both sexes (Table 2). Water consumption for the 3,200 ppm animals was barely 30% of the consumption levels for the control animals. Dose levels of 100, 200, 400, and 800 ppm were selected for the 13-week studies based on the weight gain depression observed in the 14-day studies at 800, 1,600, and 3,200 ppm.

TABLE 2. SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF RATS ADMINISTERED KING DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)			Final Body Weights Relative to Controls *(c)* (Percent)	Water Consumption Relative to Controls (Percent)
		Initial	Final	Change *(b)*		
Males						
0	5/5	240 4 ± 12 66	270 6 ± 12 30	+30 2 ± 7 79	—	—
200	5/5	221 2 ± 10 79	241 4 ± 5 75	+20 2 ± 5 99	-11	-12
400	5/5	207 8 ± 5 86	235 8 ± 7 96	+28 0 ± 4 51	-13	-18
800	5 5	230 6 ± 8 41	242 2 ± 5 13	+11 6 ± 7 54	-10	-27
1,600	5/5	226 0 ± 12 97	187 0 ± 10 22	-39 0 ± 8 47	-31	-61
3,200	5/5	223 4 ± 6 87	152 4 ± 20 74	-71 0 ± 24 94	-44	-72
Females						
0	5/5	159 4 ± 2 82	165 0 ± 3 94	+ 5 6 ± 2 01	—	—
200	5/5	145 8 ± 3 51	145 4 ± 2 93	- 0 4 ± 2 20	-12	-17
400	5/5	142 2 ± 5 82	145 4 ± 6 66	+ 3 2 ± 1 32	-12	-17
800	5/5	154 8 ± 9 44	147 4 ± 10 27	- 7 4 ± 2 40	-11	-36
1,600	5/5	170 6 ± 19 40	115 0 ± 14 53	-55 6 ± 16 45	-30	-50
3,200	5/5	149 6 ± 4 06	106 4 ± 4 93	-43 2 ± 1 66	-36	-60

(a) Number surviving/number initially in the group

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

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

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

THIRTEEN-WEEK STUDIES

No animals died. The mean final body weight was depressed 21% in male rats receiving 800 ppm, 26% in female rats receiving 800 ppm, and 6% in female rats receiving 400 ppm (Table 3). Water consumption (per kilogram of body weight) was depressed 10% or more in both sexes of rats receiving 200, 400, or 800 ppm 4,4'-methylenedianiline dihydrochloride (Table 4).

Yellowing of the pelt around the urogenital orifice was observed in 8/10 males and 9/10 females that received 800 ppm. Bile duct hyperplasia was found in all male and female rats that received 800 ppm and in 4/10 males and 3/10 females that received 400 ppm (Table 5). The extent of bile duct hyperplasia varied from partial liver involvement (20%-30%) to involvement

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)			Final Body Weights Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Males					
0	10/10	141.2 ± 3.84	294.3 ± 5.87	+153.1 ± 4.55	—
50	10/10	141.4 ± 3.75	288.8 ± 6.26	+147.4 ± 3.87	- 2
100	10/10	141.6 ± 3.51	299.5 ± 2.99	+157.9 ± 3.24	+ 2
200	10/10	141.1 ± 3.77	294.0 ± 5.06	+152.9 ± 3.68	0
400	10/10	140.6 ± 3.69	289.5 ± 5.21	+148.9 ± 4.49	- 2
800	10/10	142.0 ± 4.06	231.5 ± 6.12	+ 89.5 ± 3.89	-21
Females					
0	10/10	116.1 ± 2.88	184.8 ± 5.85	+ 68.7 ± 4.22	—
50	10/10	116.2 ± 2.98	181.1 ± 5.16	+ 64.9 ± 2.78	- 2
100	10/10	115.8 ± 2.86	188.1 ± 4.21	+ 72.3 ± 2.31	+ 2
200	10/10	115.7 ± 2.97	181.7 ± 5.56	+ 66.0 ± 2.80	- 2
400	10/10	116.2 ± 2.73	172.9 ± 4.98	+ 56.7 ± 2.72	- 6
800	10/10	115.8 ± 2.95	136.0 ± 5.39	+ 20.2 ± 3.15	-26

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

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

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

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

TABLE 4. WATER CONSUMPTION OF RATS ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR 13 WEEKS

Dose (ppm)	Water Consumption *(a)*	Water Consumption Relative to Controls *(b)* (Percent)
Males		
0	73.2	—
50	75.5	+ 3
100	70.9	- 3
200	65.9	-10
400	64.2	-12
800	48.4	-34
Females		
0	76.5	—
50	74.9	- 2
100	70.7	- 8
200	63.6	-17
400	51.0	-33
800	55.5	-27

(a) Grams water consumed/kg of body weight/day during week 12. Values are mean of consumption per cage/number of animals per cage.

(b) Water consumption Relative to Controls =

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

TABLE 5. INCIDENCES OF LESIONS OBSERVED IN RATS ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR 13 WEEKS

	Lesions *(a)*			
Dose (ppm)	Bile Duct Hyperplasia	Adenomatous Goiter	Thyroid Follicular-Cell Hyperplasia	Pituitary Basophil Hypertrophy
Males				
0	0/10	0/10	0/10	0/8
200	0/10	0/10	0/10	NE *(b)*
400	4/10	3/10	5/10	0/10
800	10/10	8/9	1/9	9/9
Females				
0	0/10	0/10	0/10	0/9
200	0/10	0/10	0/10	NE
400	3/10	1/10	7/10	0/10
800	10/10	10/10	0/10	5/9

(a) Number of lesions diagnosed/number of tissues examined.

(b) NE = Not Examined.

of nearly every portal triad. Livers contained moderate to large numbers of well-differentiated bile ducts in the portal triads and the adjacent parenchyma. In most portal triads, there was a slight increase in connective tissue and hyperplastic bile ducts were bridged between some of the portal tracts. The most severe hyperplasia bridged nearly all the portal triads with large numbers of bile ducts and ductules.

Adenomatous goiter was found in 8/9 males and 10/10 females that received 800 ppm and in 3/10 males and 1/10 females that received 400 ppm. In the group that received 800 ppm, adenomatous goiter was characterized by diffuse enlargement of both lobes and the isthmus with both diffuse papillary hyperplasia and overdistention of follicles with colloid. Follicles varied considerably in size. Marked stromal fibrosis was observed, particularly about the periphery of the thyroid. Some of the goiters contained calcified debris and sloughed epithelial cells in the colloid. The goiters were less advanced in rats that received the compound at the 400-ppm level. Some thyroid follicles had excess colloid, papillary hyperplasia, and sloughed epithelial cells. Stromal fibrosis was observed in only one female at 400 ppm in which there was a slight increase in fibrosis.

Thyroid follicular cell hyperplasia was found in 5/10 males and 7/10 females that received 400 ppm, but only in 1/9 males and 0/10 females that received 800 ppm. This early lesion was typified by follicles with wavy outlines, a few follicles moderately distended with colloid, and occasional follicles with hyperplastic buds of epithelium projecting into lumen.

Pituitary basophil hypertrophy was found in 9/9 males and 5/9 females at 800 ppm. Large pale staining cells were seen in the anterior pituitary. These were identified as basophils with the aldehyde-thionin-PAS stain. Heavily granulated and sparsely granulated basophils were recognized with this stain. Most of the basophils were of the sparsely granulated variety.

Doses selected for rats for the 2-year studies were 150 and 300 ppm 4,4'-methylenedianiline, formulated as the dihydrochloride, in the drinking water. The selection was based on body weight gain depression at levels higher than 400 ppm and histopathologic effects observed at 400 or 800 ppm (but not at 200 ppm) in the 13-week study.

TWO-YEAR STUDIES

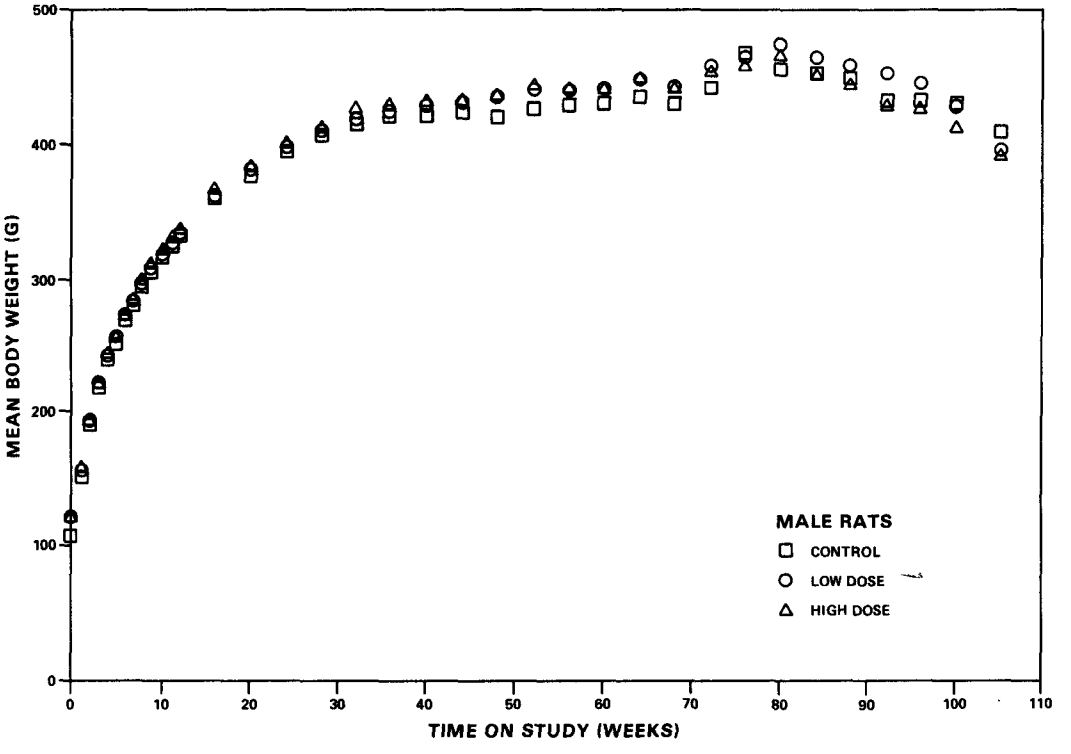
Body Weights and Clinical Signs

After week 20, mean body weights of high dose female rats were lower than those of the controls (Figure 1 and Table 6). No consistent effects on body weight were identified in the low dose females or in either dosed group of males. The average daily water consumption per rat by low- and high dose rats was 87% and 75% that of the controls for males and 93% and 82% for females (Tables 7 and 8). No compound-related clinical signs were observed.

Survival

Estimates of the probabilities of survival of male and female rats administered 4,4'-methylenedianiline dihydrochloride in the drinking water at the concentrations used in this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between any groups of either sex of rats.

In male rats, 38/50 (76%) of the controls, 41/50 (82%) of the low dose, and 40/50 (80%) of the high dose groups lived to the termination period of the study at 105-106 weeks. In female rats, 38/50 (76%) of the controls, 35/50 (70%) of the low dose, and 43/50 (86%) of the high dose groups lived to the same termination period. The survival data include one control and one low dose male rat that died during the termination period of the study. For statistical purposes, these two animals are considered to have been killed at the end of the study.



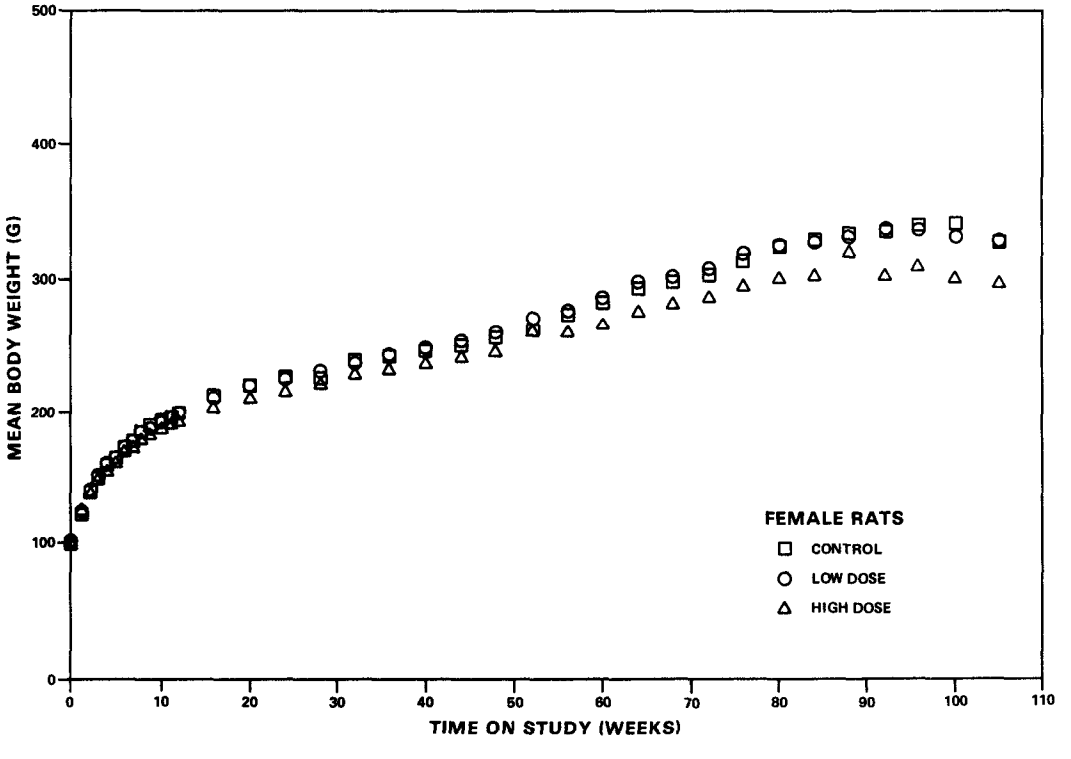


Figure 1. Growth Curves for Rats Administered Drinking Water Containing 4,4'-Methylenedianiline Dihydrochloride

TABLE 6. MEAN BODY WEIGHTS OF RATS ADMINISTERED 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE IN DRINKING WATER FOR TWO YEARS

	Mean Body Weights Change (grams)			Mean Body Weight Relative to Controls *(a)* (Percent)	
Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
0	117	122	122	+4	+ 4
1	152	156	158	+3	+ 4
20	377	382	383	+1	+ 2
40	422	428	431	+1	+ 2
60	430	442	442	+3	+ 3
80	456	475	467	+4	+ 2
100	430	429	414	0	- 4
105	410	396	392	-3	- 4
Females					
0	99	101	100	+2	+ 1
1	121	125	124	+3	+ 2
20	220	220	212	0	- 4
40	246	248	236	+1	- 4
60	283	286	266	+1	- 6
80	324	325	302	0	- 7
100	342	331	301	-3	-12
105	327	328	297	0	- 9

(a) Weight Relative to Controls = $\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$

TABLE 7. WATER AND COMPOUND CONSUMPTION OF MALE RATS ADMINISTERED 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR TWO YEARS

	Control		Low				High			
Week	Grams Water/ Day *(a)*	Body Weight (grams)	Grams Water/ Day *(a)*	Body Weight (grams)	Low/ Control *(b)*	Dose/ Day *(c)*	Grams Water Day *(a)*	Body Weight (grams)	High/ Control *(b)*	Dose/ Day *(c)*
3	25.0	217	20.9	221	0.8	14	18.9	221	0.8	26
8	27.3	295	25.4	297	0.9	13	21.1	300	0.8	21
12	27.4	332	24.6	333	0.9	11	20.9	337	0.8	19
16	29.7	360	26.4	361	0.9	11	21.6	367	0.7	18
20	28.0	377	25.9	382	0.9	10	21.1	383	0.8	17
24	28.6	395	25.3	398	0.9	10	19.4	401	0.7	15
28	28.6	407	23.1	410	0.8	8	17.4	414	0.6	13
32	24.9	415	22.6	419	0.9	8	20.1	426	0.8	14
36	27.9	422	23.6	424	0.8	8	20.1	428	0.7	14
40	26.7	422	23.6	428	0.9	8	21.6	431	0.8	15
44	26.4	424	22.0	431	0.8	8	20.1	432	0.8	14
48	26.4	420	23.6	435	0.9	8	20.7	436	0.8	14
52	26.1	426	25.6	440	1.0	9	23.1	445	0.9	16
56	29.1	428	26.9	440	0.9	9	22.3	441	0.8	15
60	28.4	430	24.6	442	0.9	8	21.6	442	0.8	15
64	28.6	435	25.1	448	0.9	8	21.4	449	0.7	14
68	31.6	430	25.1	444	0.8	8	23.7	441	0.8	16
72	27.9	443	22.9	459	0.8	7	20.0	455	0.7	13
76	30.0	468	22.9	465	0.8	7	20.1	459	0.7	13
80	26.4	456	22.1	475	0.8	7	19.6	467	0.7	13
84	27.9	454	23.1	465	0.8	7	20.9	453	0.7	14
88	29.6	450	23.7	459	0.8	8	20.7	445	0.7	14
92	23.6	433	23.1	454	1.0	8	24.1	429	1.0	17
96	27.0	433	22.1	446	0.8	7	18.6	427	0.7	13
100	30.0	430	25.4	429	0.8	9	23.6	414	0.8	17
Mean	27.7	408	24.0	416	0.9	9	20.9	414	0.8	16
SD *(d)*	1.8		1.5		0.1	2	1.6		0.1	3
CV *(e)*	6.5		6.3		11.1	22.2	7.7		12.5	18.8

(a) Grams of water consumed per animal per day. Values are mean of consumption per cage/number of animals per cage.

(b) Grams of water per day for the dosed group divided by the same value for the controls.

(c) Mg of compound consumed per day per kg of body weight.

(d) Standard Deviation

(e) Coefficient of Variation = (standard deviation/mean) x 100

TABLE 8. WATER AND COMPOUND CONSUMPTION OF FEMALE RATS ADMINISTERED 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR TWO YEARS

	Control		Low				High			
Week	Grams Water/ Day *(a)*	Body Weight (grams)	Grams Water/ Day *(a)*	Body Weight (grams)	Low/ Control *(b)*	Dose/ Day *(c)*	Grams Water Day *(a)*	Body Weight (grams)	High/ Control *(b)*	Dose/ Day *(c)*
3	16.9	148	16.3	150	1.0	16	12.1	146	0.7	25
8	19.6	183	18.7	183	1.0	15	13.9	178	0.7	23
12	17.6	199	16.6	199	0.9	12	13.3	192	0.8	21
16	18.6	213	17.6	211	0.9	12	13.0	204	0.7	19
20	17.0	220	17.4	220	1.0	12	13.7	212	0.8	19
24	18.9	227	15.9	226	0.8	11	13.0	216	0.7	18
28	17.6	226	14.9	231	0.8	10	12.9	221	0.7	17
32	16.9	239	16.4	238	1.0	10	14.0	228	0.8	18
36	17.3	243	14.7	244	0.9	9	13.6	233	0.8	17
40	17.6	246	16.6	248	0.9	10	14.0	236	0.8	18
44	15.4	251	15.1	254	1.0	9	13.9	241	0.9	17
48	19.1	256	16.0	260	0.8	9	14.3	246	0.7	17
52	19.3	263	17.7	272	0.9	10	16.3	263	0.8	19
56	20.9	274	18.7	276	0.9	10	17.4	260	0.8	20
60	19.9	283	18.7	286	0.9	10	16.9	266	0.8	19
64	20.7	294	19.6	298	0.9	10	17.6	276	0.8	19
68	22.1	298	19.7	302	0.9	10	17.6	283	0.8	19
72	20.7	304	19.9	308	1.0	10	17.9	286	0.9	19
76	20.7	355	19.4	319	0.9	9	18.3	329	0.9	17
80	21.0	324	20.1	325	1.0	9	19.1	302	0.9	19
84	22.6	329	21.6	328	1.0	10	20.1	304	0.9	20
88	21.6	334	19.9	331	0.9	9	18.6	318	0.9	18
92	17.0	335	19.4	337	1.1	9	16.4	304	1.0	16
96	22.0	340	19.3	336	0.9	9	18.6	310	0.8	18
100	23.9	342	21.1	331	0.9	10	20.6	301	0.9	21
Mean	19.4	269	18.1	269	0.9	10	15.9	254	0.8	19
SD *(d)*	2.2		2.0		0.1	2	2.6		0.1	2
CV *(e)*	11.3		11.0		11.1	20.0	16.4		12.5	10.5

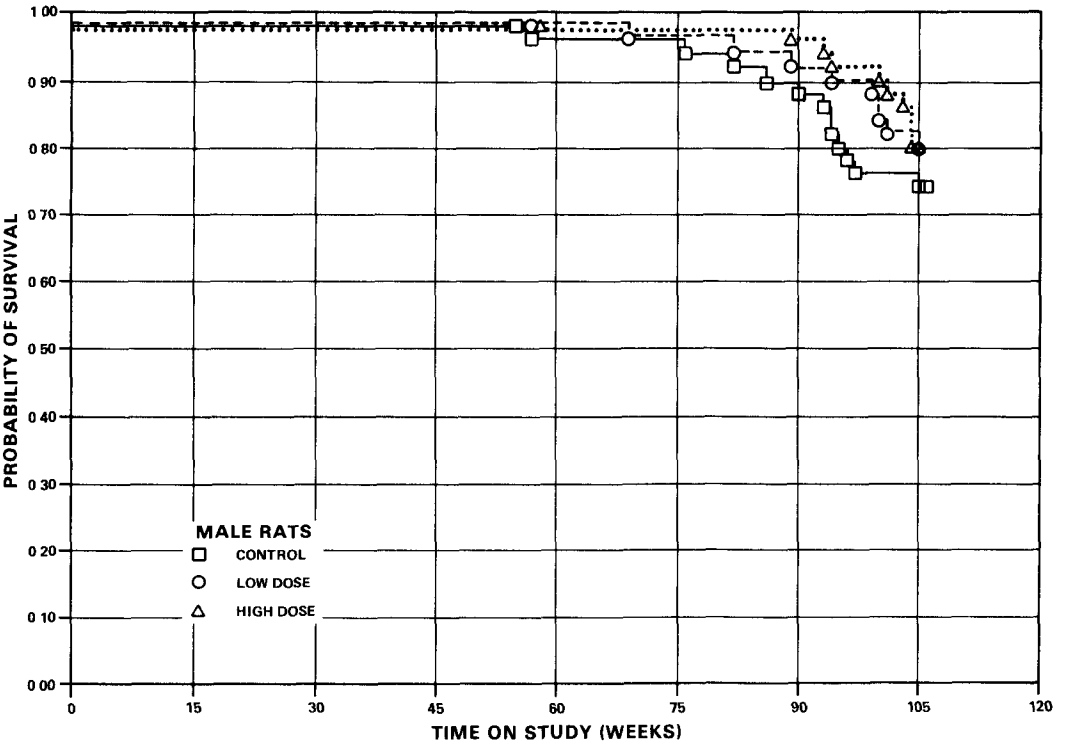
(a) Grams of water consumed per animal per day. Values are mean of consumption per cage/number of animals per cage.

(b) Grams of water per day for the dosed group divided by the same value for the controls.

(c) Mg of compound consumed per day per kg of body weight.

(d) Standard Deviation

(e) Coefficient of Variation = (standard deviation/mean) x 100



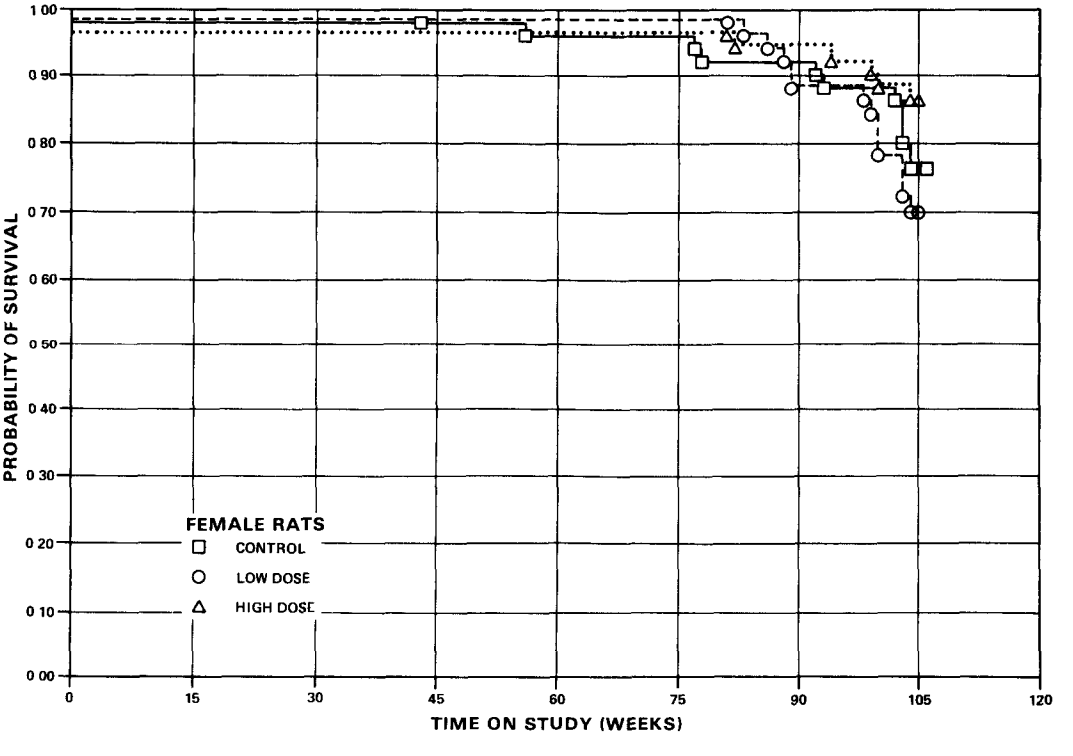


Figure 2. Survival Curves for Rats Administered Drinking Water Containing 4,4'-Methylenedianiline Dihydrochloride

Pathology and Statistical Analysis of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2 for males and females, respectively; Appendix Tables A3 and A4 give the survival and tumor status for each individual animal in the male rat and female rat studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Historical incidences of tumors in control animals are listed in Appendix E. Appendix F, Tables F1 and F2, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in chapter II (Data Recording and Statistical Methods) and Appendix F (footnotes). Incidences of animals with primary tumors which were not statistically significant are listed in Table 13.

Thyroid: Follicular and C-cell lesions were observed at the incidences shown in Table 9.

A distended follicle having eosinophilic or pale colloid and lined by cuboidal epithelial cells was considered a follicular cyst. Papillary ingrowths of the epithelium, resulting in follicles of varying sizes, were characteristic of follicular hyperplasia. The number of epithelial cells was increased.

Follicular neoplasms were well vascularized. The capsule was prominent only in a few tumors. Some of the capsular arteries were sclerotic. Follicular adenoma compressed the normal tissue. Both macro- and micro-follicular variants were common. The cells were columnar or cuboidal. The mixed papillary-follicular carcinoma seen in nine dosed rats involved one or both lobes. The papillary-follicular pattern and back-to-back cell arrangement with scant stroma in between were common. Cells were crowded in areas. Nuclei were hyperchromatic. Mitotic figures were not numerous. The carcinoma had infiltrated into the capsule in nine dosed rats and into the blood vessel in one rat.

TABLE 9. INCIDENCES OF RATS WITH NEOPLASTIC OR NONNEOPLASTIC LESIONS OF THE THYROID

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
No. of Thyroid Glands Evaluated	49	47	48	47	47	48
Follicular Cell						
Cyst	1	2	3	0	3	7
Hyperplasia	1	2	3	1	3	8
Adenoma	1	4	3	0	2	17
Carcinoma	0	0	7	0	2	2
C-Cell						
Hyperplasia	4	2	1	5	3	4
Adenoma	1	2	1	0	3	6
Carcinoma	2	0	1	1	2	1

III. RESULTS: RATS—TWO-YEAR STUDIES

In male rats, follicular cell carcinomas occurred with a statistically significant positive trend, and the incidence in the high dose group was significantly higher than those in the controls (Table 10). Follicular cell adenomas (Table 13) were increased in dosed groups relative to controls, but none of the results of statistical tests were significant. The combination of follicular cell adenoma or carcinoma was significantly elevated in high dose male rats.

In female rats, follicular cell adenomas were observed with a statistically significant positive trend (Table 10). The incidence of follicular cell adenoma in the high dose group was significantly higher than that in the controls. No follicular cell carcinomas were seen in the control group, but two were found in each dosed group.

C-cell adenomas of the thyroid occurred in female rats, but not in male rats, with a statistically significant positive trend (Table 10). The incidences in the high dose group were significantly higher than those in the controls.

TABLE 10. INCIDENCES OF RATS WITH THYROID TUMORS

	Vehicle Control	Low Dose	High Dose
Males			
Follicular Cell Adenoma			
Tumor Rates			
Overall Incidence	1/49 (2%)	4/47 (9%)	3/48 (6%)
Adjusted Incidence	2.6%	9.4%	7.1%
Terminal Incidence	1/38 (3%)	2/40 (5%)	2/40 (5%)
Life Table	P=0.293	P=0.208	P=0.338
Incidental Tumor Test	P=0.264	P=0.166	P=0.321
Cochran-Armitage Trend Test	P=0.245		
Fisher Exact Test		P=0.168	P=0.301
Follicular Cell Carcinoma			
Overall Incidence	0/49 (0%)	0/47 (0%)	7/48 (15%)
Adjusted Incidence	0.0%	0.0%	17.0%
Terminal Incidence	0/38 (0%)	0/40 (0%)	6/40 (15%)
Life Table Test	P=0.001	*(a)*	P=0.012
Incidental Tumor Test	P=0.001	*(a)*	P=0.011
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		*(a)*	P=0.006
Follicular Cell Adenoma or Carcinoma			
Overall Incidence	1/49 (2%)	4/47 (9%)	10/48 (21%)
Adjusted Incidence	2.6%	9.4%	23.6%
Terminal Incidence	1/38 (3%)	2/40 (5%)	8/40 (20%)
Life Table Test	P=0.004	P=0.208	P=0.008
Incidental Tumor Test	P=0.003	P=0.166	P=0.007
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.168	P=0.003

TABLE 10. INCIDENCES OF RATS WITH THYROID TUMORS (Continued)

	Vehicle Control	Low Dose	High Dose
Females			
Follicular Cell Adenoma			
Overall Incidence	0/47 (0%)	2/47 (4%)	17/48 (35%)
Adjusted Incidence	0.0%	5.3%	37.7%
Terminal Incidence	0/36 (0%)	1/35 (3%)	15/43 (35%)
Life Table Test	P<0.001	P=0.226	P<0.001
Incidental Tumor Test	P<0.001	P=0.220	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.247	P<0.001
Follicular Cell Adenoma or Carcinoma			
Overall Incidence	0/47 (0%)	4/47 (9%)	19/48 (40%)
Adjusted Incidence	0.0%	10.1%	42.1%
Terminal Incidence	0/36 (0%)	2/35 (6%)	17/43 (40%)
Life Table Test	P<0.001	P=0.062	P<0.001
Incidental Tumor Test	P<0.001	P=0.099	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.058	P<0.001
C-Cell Adenoma			
Overall Incidence	0/47 (0%)	3/47 (6%)	6/48 (13%)
Adjusted Incidence	0.0%	8.6%	14.0%
Terminal Incidence	0/36 (0%)	3/35 (9%)	6/43 (14%)
Life Table Test	P=0.020	P=0.116	P=0.029
Incidental Tumor Test	P=0.020	P=0.116	P=0.029
Cochran-Armitage Trend Test	P=0.011		
Fisher Exact Test		P=0.121	P=0.014
C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall Incidence	1/47 (2%)	5/47 (11%)	7/48 (15%)
Adjusted Incidence	2.3%	14.3%	16.3%
Terminal Incidence	0/36 (0%)	5/35 (14%)	7/43 (16%)
Life Table Test	P=0.048	P=0.096	P=0.054
Incidental Tumor Test	P=0.035	P=0.094	P=0.032
Cochran-Armitage Trend Test	P=0.027		
Fisher Exact Test		P=0.102	P=0.032

(a) Not significant. No tumors in control or low-dose groups.

Liver: Nonneoplastic lesions in the liver, observed at higher incidences in dosed males than in controls, included unspecified dilatation (control, 1/50, 2%; low dose, 6/50, 12%; high dose, 10/50, 20%), fatty metamorphosis (14/50, 28%; 28/50, 56%; 33/50, 66%) and focal cellular change (14/50, 28%; 38/50, 76%; 36/50, 72%). In female rats both fatty metamorphosis (7/50, 14%; 20/50, 40%; 11/50, 22%) and focal cellular change (5/50, 10%; 17/50, 34%; 10/50, 20%) were also elevated in dosed groups versus controls.

Neoplastic nodules in male rats occurred with a statistically significant positive trend and the incidences were significantly higher in the low dose and high dose groups than in the controls (Table 11). The incidences of neoplastic nodules in dosed female rats were higher than those in the controls, but the increases were not statistically significant (control, 4/50, 8%; low dose, 8/50, 16%; high dose, 8/50, 16%).

In the livers of some dosed rats, the occurrence of more than one neoplastic nodule suggested a multicentric origin. The nodules varied in size and compressed the adjacent tissue. Lobular architecture was not maintained. Sinusoids were distended. Cytoplasmic staining varied. Nuclei had granular chromatin. Hepatocellular carcinoma involved a part or an entire lobe of the liver. Delicate fibrovascular septa had dissected the tumor parenchyma into nodules. The large cells had an eosinophilic or vacuolated cytoplasm. Nuclei were hyperchromatic and had prominent nucleoli. Varying degrees of cystic degeneration were found in these neoplasms. The cysts contained a lacy material (some of which stained blue) and a few blood cells.

TABLE 11. INCIDENCES OF MALE RATS WITH NEOPLASTIC NODULES OF THE LIVER

	Control	Low Dose	High Dose
Overall Incidence	1/50 (2%)	12/50 (24%)*(a)*	25/50 (50%)
Adjusted Incidence	2.6%	29.3%	56.6%
Terminal Incidence	1/38 (3%)	12/41 (29%)	21/40 (53%)
Life Table Test	P<0.001	P=0.002	P<0.001
Incidental Tumor Test	P<0.001	P=0.002	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.001	P<0.001

(a) One additional rat had a hepatocellular carcinoma.

Bile Duct: A bile duct adenoma was found in one high dose male rat. This tumor had not been previously diagnosed in 3,633 control male F344/N rats in the Bioassay Program.

Urinary Bladder: Transitional cell papillomas were found in 2/50 (4%) low dose and 1/50 (2%) high dose female rats. This tumor has been observed in only 3 of 3,644 untreated control female rats in the Bioassay Program (Appendix E, Table E7).

Ovary: Granulosa cell tumors were found in 2/50 high dose females and 3/50 low dose females. A granulosa cell carcinoma was found in a fourth low dose female. No granulosa cell tumors were identified in the controls. Among control female rats in the Bioassay Program, only 11/3,642 (0.31%) had granulosa cell tumors and 1/3,642 (0.3%) had granulosa cell carcinomas (Appendix E, Table E6).

Kidney: Mineralization of the kidney was observed in increased incidence in high dose males when compared with that in the controls (control, 9/50, 18%; low dose, 10/50, 20%; high dose, 19/50, 38%).

Hematopoietic System: In male rats, leukemia occurred with significant negative trends (Table 12). Results of the pairwise comparisons between the control and high dose groups were significant in the life table test. This tumor was not observed in significant proportions in female rats. (See Appendix E, Table E5 for historical incidences in controls.)

TABLE 12. INCIDENCES OF MALE RATS WITH LEUKEMIA

	Control	Low Dose	High Dose
Overall Incidence	12/50 (24%)	6/50 (12%) *(a)*	5/50 (10%)
Adjusted Incidence	27.9%	14.6%	11.8%
Terminal Incidence	8/38 (21%)	6/41 (15%)	3/40 (8%)
Life Table Test	P=0.029N	P=0.077N	P=0.048N
Incidental Tumor Test	P=0.036N	P=0.103N	P=0.059N
Cochran-Armitage Trend Test	P=0.036N		
Fisher Exact Test		P=0.096N	P=0.054N

(a) One additional rat had a lymphoma.

TABLE 13. INCIDENCES OF RATS WITH PRIMARY TUMORS THAT OCCURRED WITHOUT SIGNIFICANT GROUP DIFFERENCES *(a)*

	Control	Low Dose	High Dose
Males			
Adrenal: Pheochromocytoma	7/50 (14%) *(b)*	5/49 (10%)	5/49 (10%)
Hematopoietic System: Myelo-monocytic Leukemia	9/50 (18%)	6/50 (12%)	5/50 (10%)
Lung: Alveolar/Bronchiolar Adenoma	2/50 (4%)	3/50 (6%)	4/50 (8%) *(c)*
Pancreas: Islet Cell Adenoma	2/49 (4%)	4/49 (8%)	3/47 (6%)
Pituitary: Adenoma	24/46 (52%)	20/47 (43%)	21/49 (43%)
Carcinoma	1/46 (2%)	2/47 (4%)	1/49 (2%)
Preputial Gland: Adenoma	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adenoma or Carcinoma	4/50 (8%)	0/50 (0%)	3/50 (6%)
Subcutaneous Tissue: Fibroma	5/50 (10%)	1/50 (2%)	2/50 (4%)
Skin: Squamous Cell Papilloma	0/50 (0%) *(d)*	4/50 (8%)	1/50 (2%)
Testis: Interstitial Cell Tumor	42/49 (86%)	42/50 (84%)	47/50 (94%) *(e)*
Thyroid: Follicular Cell Adenoma	1/49 (2%)	4/47 (9%)	3/48 (6%)
C-Cell Adenoma or Carcinoma	3/49 (6%)	2/47 (4%)	2/48 (4%)
Females			
Clitoral Gland: Adenoma	2/50 (4%) *(f)*	4/50 (8%)	5/50 (10%)
Hematopoietic System: Myelo-monocytic Leukemia	3/50 (6%)	7/50 (14%)	2/50 (4%)
Liver: Neoplastic Nodule	4/50 (8%)	8/50 (16%)	8/50 (16%)
Mammary Gland: Fibroadenoma	10/50 (20%)	14/50 (28%)	9/50 (18%)
Adenocarcinoma	4/50 (8%)	4/50 (8%)	0/50 (0%)
Ovary: Granulosa Cell Tumor	0/50 (0%)	3/50 (6%)	2/50 (4%)
Pituitary: Adenoma	31/49 (63%)	25/49 (51%)	34/49 (69%)
Carcinoma	0/49 (0%)	2/49 (4%)	3/49 (6%)
Skin or Subcutaneous Tissue: Sarcoma or Fibrosarcoma	2/50 (4%)	0/50 (0%)	3/50 (6%)
Uterus: Endometrial Stromal Polyp	11/48 (23%)	15/50 (30%)	12/50 (24%)
Sarcoma	3/48 (6%)	0/50 (0%)	1/50 (2%)

(a) Primary tumors that occurred at an incidence of at least 5% but were not significant by statistical analyses.
(b) One malignant pheochromocytoma occurred in this group.
(c) One alveolar/bronchiolar carcinoma was observed in this group.
(d) One squamous cell carcinoma was observed in this group.
(e) One malignant interstitial cell tumor was observed in this group.
(f) One carcinoma was observed in this group.

FOURTEEN-DAY STUDIES

All mice that received 3,200 ppm died (Table 14). Three of five males and 2/5 females that received 1,600 ppm and 2/5 males and 1/5 females that received 800 ppm also died. Mice that received 800 ppm or more failed to gain weight. No compound-related lesions were identified at necropsy.

Water consumption (Table 14) was depressed 29% and 79% in male mice that received 1,600 or 3,200 ppm and 15%, 45%, and 79% in female mice that received 800, 1,600, or 3,200 ppm, respectively.

TABLE 14. SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF MICE ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)			Final Body Weights Relative to Controls *(c)* (Percent)	Water Consumption Relative to Controls (Percent)
		Initial	Final	Change *(b)*		
Males						
0	5/5	26.8 ± 0.37	27.8 ± 0.66	+ 1.0 ± 0.45		
200	5/5	26.8 ± 0.37	28.6 ± 0.68	+ 1.8 ± 0.49	+ 3	+ 6
400	5/5	26.8 ± 0.37	27.4 ± 0.68	+ 0.6 ± 0.40	- 1	+ 29
800	3/5	27.0 ± 0.58	26.3 ± 0.67	- 0.7 ± 0.33	- 5	+ 13
1,600	2/5	26.0 ± 1.00	24.0 ± 2.00	- 2.0 ± 3.00	-14	-29
3,200	0/5	*(d)*	*(d)*	*(d)*		- 79
Females						
0	5/5	21.0 ± 0.71	22.2 ± 0.37	+ 1.2 ± 0.37		
200	5/5	22.4 ± 1.03	22.2 ± 0.73	- 0.2 ± 1.24	0	- 1
400	5/5	21.4 ± 0.51	23.0 ± 0.84	+ 1.6 ± 0.68	+ 4	- 5
800	4/5	20.8 ± 1.31	20.8 ± 1.11	0.0 ± 0.41	- 6	- 15
1,600	3/5	21.3 ± 0.67	18.7 ± 0.33	- 2.6 ± 0.33	-16	- 45
3,200	0/5	*(d)*	*(d)*	*(d)*		- 79

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.
(b) Mean weight change of the survivors of the group ± standard error of the mean.
(c) Weight of the dosed group relative to that of the controls =

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

(d) No data are presented due to the 100% mortality in this group.

THIRTEEN-WEEK STUDIES

No mice died during the dosing period. The mean final body weight was depressed 7% or more in male and female mice that received 400 ppm and in male mice that received 200 ppm (Table 15).

Water consumption of dosed male mice was greater than that of the controls (Table 16). Water consumption of dosed female mice was comparable to that for the control female mice.

Bile duct hyperplasia of moderate severity was found in 5/10 males and 4/10 females that received 400 ppm; it was not observed in control mice. Adenomatous goiters (less severe in mice than those found in high dose rats) were not detected in any control mice but were observed in 1/10 males and 1/10 females that received 400 ppm. Distention of the follicles with colloid, papillary hyperplasia, and vacuolation of the colloid were observed in the goiters.

Doses selected for both sexes of mice in the 2-year studies were 150 and 300 ppm 4,4'-methylenedianiline, formulated as dihydrochloride, in drinking water. The weight gain depression and the lack of clinical signs of toxicity were the bases of dose selection.

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)			Final Body Weights Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Males					
0	10/10	22.5 ± 0.55	34.2 ± 1.39	+11.7 ± 0.94	
25	10/10	22.5 ± 0.55	34.8 ± 1.21	+12.3 ± 0.86	+ 2
50	10/10	22.4 ± 0.51	34.3 ± 1.20	+11.9 ± 0.84	0
100	10/10	22.6 ± 0.49	34.3 ± 1.23	+11.7 ± 0.79	0
200	10/10	22.7 ± 0.49	31.7 ± 1.34	+ 9.0 ± 0.93	- 7
400	10/10	22.6 ± 0.53	29.6 ± 0.55	+ 7.0 ± 0.32	-13
Females					
0	10/10	17.5 ± 0.35	25.4 ± 0.57	+ 7.9 ± 0.34	
25	10/10	17.2 ± 0.37	25.5 ± 0.55	+ 8.3 ± 0.38	0
50	10/10	17.7 ± 0.31	26.6 ± 0.51	+ 8.9 ± 0.40	+ 5
100	10/10	17.6 ± 0.33	26.1 ± 0.67	+ 8.5 ± 0.56	+ 3
200	10/10	17.6 ± 0.45	25.8 ± 0.89	+ 8.2 ± 0.53	+ 2
400	10/10	17.5 ± 0.28	23.7 ± 0.65	+ 6.2 ± 0.58	- 7

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

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

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

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

TABLE 16. WATER CONSUMPTION OF MICE ADMINISTERED WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR 13 WEEKS

Dose (ppm)	Water Consumption *(a)*	Water Consumption Relative to Controls *(b)* (Percent)
Males		
0	89.4	
25	101.7	+14
50	114.4	+28
100	114.1	+28
200	132.5	+48
400	137.3	+54
Females		
0	140.0	
25	141.5	+ 1
50	152.3	+ 9
100	144.0	+ 3
200	129.3	- 8
400	130.0	- 7

(a) Grams water consumed/kg of body weight/day. Values are mean of consumption per cage/number of animals per cage.

(b) Water consumption relative to controls = $\frac{\text{(Dosed Group) - (Control Group)}}{\text{(Control Group)}} \times 100$

TWO-YEAR STUDIES

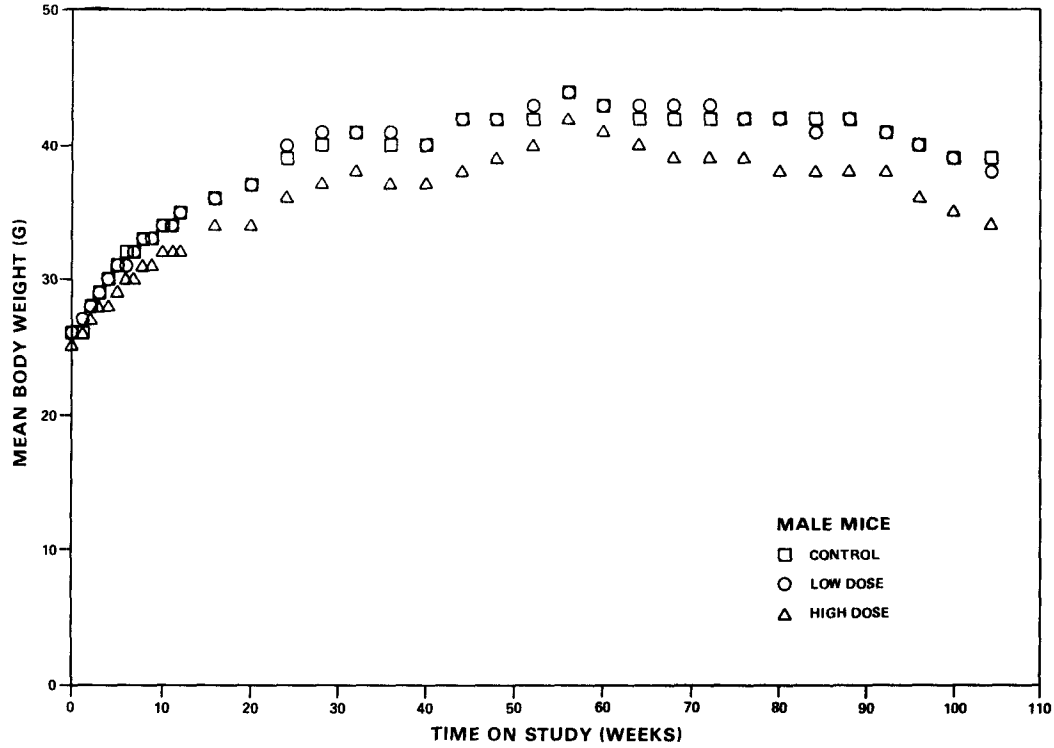
Body Weights and Clinical Signs

Mean body weights of high dose mice of either sex were lower than those of the controls throughout most of the study (Figure 3 and Table 17); this difference was first noticeable by week 16. The average daily water consumption per mouse by low and high dose mice was 106% and 111% that of the controls for males and 87% and 96% for females (Tables 18 and 19). No other compound-related clinical signs were observed.

Survival

Estimates of the probabilities of survival of male and female mice administered 4,4'-methylenedianiline dihydrochloride in the drinking water at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 4. The survival of the high dose group of male mice was significantly reduced when compared with both that of the low dose (P=0.040) and the control groups (P=0.006). No other significant differences in survival were observed between any groups of either sex.

In male mice, 40/50 (80%) of the controls, 39/50 (78%) of the low dose, and 32/50 (64%) of the high dose group lived to the termination period of the study at 104-105 weeks. In female mice, 40/50 (80%) of the controls, 38/50 (76%) of the low dose, and 37/50 (74%) of the high dose group lived to the same termination period. The survival data include one control, one low dose, and five high dose males and two control, one low dose, and one high dose females that died during the termination period of the study. For statistical purposes these animals are considered to have been killed at the end of the study.



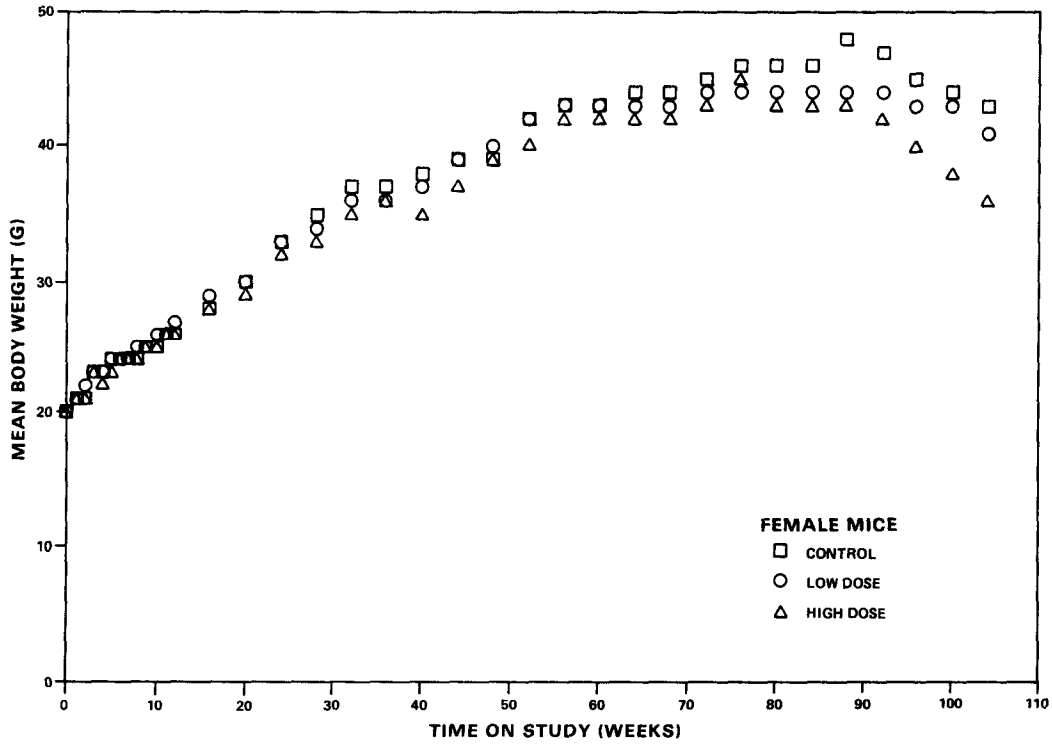


Figure 3. Growth Curves for Mice Administered Drinking Water Containing 4,4'-Methylenedianiline Dihydrochloride

TABLE 17. MEAN BODY WEIGHTS OF MICE ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR TWO YEARS

Week No.	Mean Body Weights Change (grams)			Mean Body Weights Relative to Controls *(a)* (Percent)	
	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
0	26	26	25	0	- 4
1	26	27	26	+4	0
20	37	37	34	0	- 8
40	40	40	37	0	- 8
60	43	43	41	0	- 5
80	42	42	42	0	0
100	39	39	35	0	-10
104	39	38	34	-3	-13
Females					
0	20	20	20	0	0
1	21	21	21	0	0
20	30	30	29	0	- 3
40	38	37	35	-3	- 8
60	43	43	42	0	- 2
80	46	44	43	-4	- 7
100	44	43	38	-2	-14
104	43	41	36	-5	-16

(a) Weight relative to controls =

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

TABLE 18. WATER AND COMPOUND CONSUMPTION OF MALE MICE ADMINISTERED 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR TWO YEARS

	Control		Low				High			
Week	Grams Water/ Day *(a)*	Body Weight (grams)	Grams Water/ Day *(a)*	Body Weight (grams)	Low/ Control *(b)*	Dose/ Day *(c)*	Grams Water Day *(a)*	Body Weight (grams)	High/ Control *(b)*	Dose/ Day *(c)*
4	7.1	30	6.9	30	1.0	34	7.9	28	1.1	84
9	8.1	33	7.6	33	0.9	34	6.9	31	0.8	66
12	8.0	35	8.4	35	1.1	36	6.9	32	0.9	64
16	7.6	36	8.1	36	1.1	34	8.1	34	1.1	72
20	7.0	37	7.0	37	1.0	28	7.0	34	1.0	62
24	8.4	39	5.3	40	0.6	20	6.9	36	0.8	57
28	7.1	40	6.1	41	0.9	22	8.1	37	1.1	66
32	6.6	41	6.1	41	0.9	22	6.1	38	0.9	48
36	6.3	40	6.9	41	1.1	25	7.0	37	1.1	57
40	5.3	40	6.4	40	1.2	24	7.1	37	1.4	58
44	5.9	42	9.1	42	1.6	33	6.6	38	1.1	52
48	5.6	42	6.0	42	1.1	21	5.9	39	1.1	45
52	5.1	42	6.0	43	1.2	21	5.9	40	1.1	44
56	5.9	44	6.0	44	1.0	20	6.3	42	1.1	45
60	6.6	43	5.3	43	0.8	18	6.4	41	1.0	47
64	5.9	42	6.3	43	1.1	22	6.1	40	1.0	46
68	6.3	42	6.7	43	1.1	23	6.1	39	1.0	47
72	5.7	42	6.6	43	1.2	23	7.1	39	1.3	55
76	5.9	42	7.1	42	1.2	26	7.6	39	1.3	58
80	5.9	42	6.6	42	1.1	23	7.1	38	1.2	56
84	6.1	42	7.0	41	1.1	26	7.7	38	1.3	61
88	6.0	42	6.6	42	1.1	23	7.4	38	1.2	59
92	6.1	41	6.9	41	1.1	25	7.7	38	1.3	61
96	5.3	40	5.9	40	1.1	22	6.9	36	1.3	57
100	4.3	39	6.1	39	1.4	24	7.3	35	1.7	62
Mean	6.3	40	6.7	40	1.1	25	7.0	37	1.1	57
SD *(d)*	1.0		0.9		0.2	5	0.7		0.2	9
CV *(e)*	15.9		13.4		18.2	20.0	10.0		18.2	15.8

(a) Grams of water consumed per animal per day. Values are mean of consumption per cage/number of animals per cage.

(b) Grams of water per day for the dosed group divided by the same value for the controls.

(c) Mg of compound consumed per day per kg of body weight.

(d) Standard Deviation

(e) Coefficient of Variation = (standard deviation/mean) x 100

TABLE 19. WATER AND COMPOUND CONSUMPTION OF FEMALE MICE ADMINISTERED 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR TWO YEARS

	Control		Low				High			
Week	Grams Water/ Day *(a)*	Body Weight (grams)	Grams Water/ Day *(a)*	Body Weight (grams)	Low/ Control *(b)*	Dose/ Day *(c)*	Grams Water Day *(a)*	Body Weight (grams)	High/ Control *(b)*	Dose/ Day *(c)*
4	4.6	23	4.9	23	1.1	32	4.6	22	1.0	62
9	5.9	25	4.9	25	0.8	29	5.1	25	0.9	62
12	6.7	26	6.1	27	0.9	34	5.7	26	0.9	66
16	5.6	28	5.6	29	1.0	29	4.6	28	0.8	49
20	5.0	30	4.0	30	0.8	20	5.0	29	1.0	52
24	6.0	33	4.9	33	0.8	22	4.4	32	0.7	42
28	5.0	35	6.1	34	1.2	27	5.3	33	1.1	48
32	5.6	37	4.9	36	0.9	20	4.9	35	0.9	42
36	5.3	37	6.0	36	1.1	25	4.9	36	0.9	40
40	6.0	38	4.1	37	0.7	17	4.6	35	0.8	39
44	5.1	39	4.1	39	0.8	16	4.6	37	0.9	37
48	4.1	39	3.9	40	0.9	14	4.1	39	1.0	32
52	5.1	42	4.0	42	0.8	14	3.9	40	0.8	29
56	5.9	43	4.0	43	0.7	14	4.1	42	0.7	30
60	5.1	43	4.4	43	0.9	15	4.6	42	0.9	33
64	7.6	44	4.1	43	0.5	14	4.6	42	0.6	33
68	5.4	44	4.1	44	0.8	14	5.1	42	0.9	37
72	5.0	45	3.3	44	0.7	11	5.1	43	1.0	36
76	4.7	46	4.9	44	1.0	17	5.9	45	1.2	39
80	4.7	46	4.4	44	0.9	15	5.3	43	1.1	37
84	5.3	46	4.4	44	0.8	15	5.9	43	1.1	41
88	5.1	48	4.3	44	0.8	15	5.7	43	1.1	40
92	5.6	47	4.6	44	0.8	16	7.1	42	1.3	51
96	4.0	45	4.1	43	1.0	14	5.9	40	1.5	44
100	4.1	44	3.9	43	0.9	13	6.3	38	1.5	50
Mean	5.3	39	4.6	38	0.9	19	5.1	37	1.0	43
SD *(d)*	0.8		0.7		0.2	7	0.8	0.2	10	
CV *(e)*	15.1		15.2		22.2	36.8	15.7		20.0	23.3

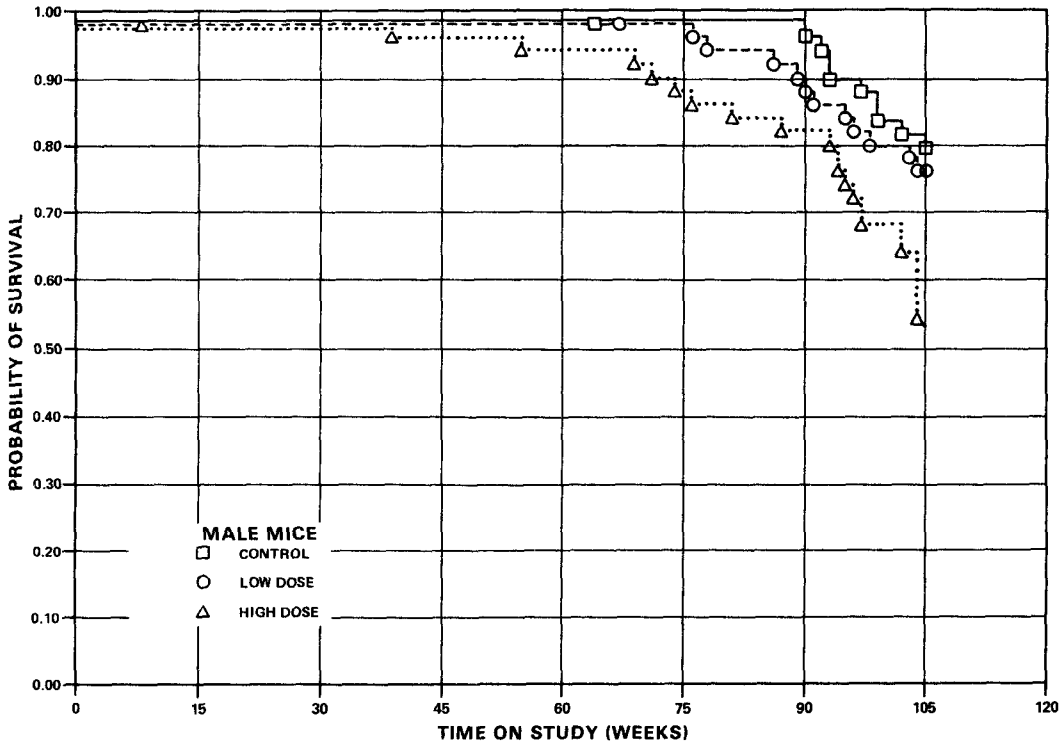
(a) Grams of water consumed per animal per day. Values are mean of consumption per cage/number of animals per cage.

(b) Grams of water per day for the dosed group divided by the same value for the controls.

(c) Mg of compound consumed per day per kg of body weight.

(d) Standard Deviation

(e) Coefficient of Variation = (standard deviation/mean) x 100



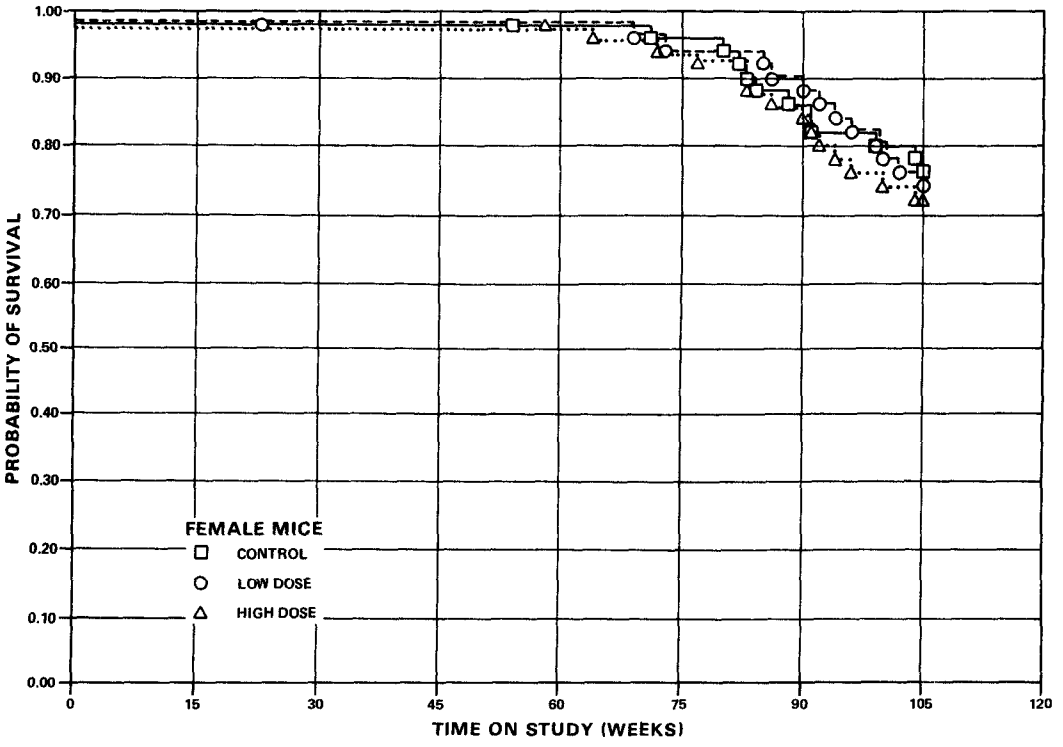


Figure 4. Survival Curves for Mice Administered Drinking Water Containing 4,4'-Methylenedianiline Dihydrochloride

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. Historical incidences of tumors in control animals are listed in Appendix E. Appendix F, Tables F3 and F4 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in chapter II (Data Recording and Statistical Methods) and Appendix F (footnotes). Incidences of animals with primary tumors which were not statistically significant are listed in Table 27.

Thyroid: The incidences of mice with neoplastic or nonneoplastic lesions of the thyroid are presented in Table 20. Histologic appearances of the lesions are described below.

A markedly distended follicle containing eosinophilic or pale colloid and lined by epithelial cells was considered to be a follicular cyst. Follicular hyperplasia was characterized by a papillary ingrowth of the epithelium resulting in follicles of varying sizes. The number of epithelial cells was increased. In many mice, there was more than one area of hyperplasia, thus suggesting a multicentric origin.

The adenomas compressed the adjacent tissue. Follicular arrangement was maintained in many neoplasms, and in one or two there was a solid sheet of cells. The cells were columnar or cuboidal, and the cytoplasm was basophilic. Nuclei had stippled chromatin. Two of the neoplasms in female mice were considered carcinomas; they had grown out of the capsule. Inflammatory cells, cholesterol clefts, and stromal reaction were present in a few neoplasms.

Follicular cell adenomas in males and females occurred with statistically significant positive trends and the incidences in the high dose groups were significantly greater than those in the controls (Table 21).

TABLE 20. INCIDENCES OF MICE WITH NEOPLASTIC OR NONNEOPLASTIC LESIONS OF THE THYROID

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Thyroid Glands Examined	47	49	49	50	47	50
Follicular Cell						
Cyst	0	0	2	1	0	0
Hyperplasia	0	3	18	0	0	23
Adenoma	0	3	16	0	1	13
Carcinoma	0	0	0	0	0	2

TABLE 21. INCIDENCES OF MICE WITH FOLLICULAR CELL ADENOMAS OF THE THYROID

	Vehicle Control	Low Dose	High Dose
Males			
Overall Incidence	0/47 (0%)	3/49 (6%)	16/49 (33%)
Adjusted Incidence	0.0%	7.0%	42.8%
Terminal Incidence	0/39 (0%)	1/38 (3%)	11/32 (34%)
Life Table Test	P<0.001	P=0.118	P<0.001
Incidental Tumor Test	P<0.001	P=0.146	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.129	P<0.001
Females			
Overall Incidence	0/50 (0%)	1/47 (2%)	13/50 (26%) *(a)*
Adjusted Incidence	0.0%	2.7%	32.9%
Terminal Incidence	0/40 (0%)	1/37 (3%)	11/37 (30%)
Life Table Test	P<0.001	P=0.484	P<0.001
Incidental Tumor Test	P<0.001	P=0.484	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.485	P<0.001

(a) Follicular cell carcinoma was found in two additional females. Statistical tests for adenoma or carcinoma (combined) were P<0.001.

Liver: Hepatocellular carcinoma in both sexes of mice occurred with statistically significant positive trends. The incidences of hepatocellular carcinomas in the dosed males and high dose females were significantly higher than those in the controls (Table 22). The incidence of hepatocellular adenomas was also significantly elevated in the high dose females.

Hepatocellular adenomas compressed the adjacent liver tissue. Cytoplasm of the cells was acidophilic or vacuolated. Nuclei were hyperchromatic. Hepatocellular carcinoma involved a part or an entire lobe of the liver. Some neoplasms were surrounded either by fibrous septa or by blood vessels. Nodules within nodules were found in a few tumors. Cells were large and arranged in acinar or trabecular patterns or were present in solid sheets. Cytoplasmic staining varied. Glassy pink inclusions were present in some cells. Nuclei varied in shape and size. Chromatin was coarse or stippled, and one to two nucleoli were present. Both normal and abnormal mitotic figures were numerous. A few nuclei had inclusions, and there were some cells with bizarre nuclei.

Distended sinusoids or cavernous vascular spaces were lined by fusiform cells in some neoplasms. These cells occasionally surrounded transformed hepatocytes. Such changes suggested an angiomatous transformation.

Necrosis, inflammatory cells, macrophages, hemorrhage, and mineralization were common in large tumors. Hepatocellular carcinoma had metastasized to the lungs in eight mice (four control males, one low dose male, one low dose female, and two high dose males).

Liver degeneration was observed in 40/50 (80%) low dose males, in 30/50 (60%) high dose males, and in 7/50 (14%) high dose females, but in none of the control mice.

In the livers of many dosed mice, islands of hepatocytes were enlarged and appeared to have undergone degenerative changes. These included loss of cytoplasmic basophilia, clumping of cytoplasmic material, eosinophilic inclusions, lipid vacuoles, and occasional absence of nuclei. Clusters of golden brown pigment were present in areas. Adjacent to such areas were foci of large hepatocytes with a granular eosinophilic cytoplasm and nuclei with stippled chromatin and one to two nucleoli.

TABLE 22. INCIDENCES OF MICE WITH LIVER TUMORS

	Vehicle Control	Low Dose	High Dose
Males			
Hepatocellular Carcinoma			
Overall Incidence	10/49 (20%)	33/50 (66%)	29/50 (58%)
Adjusted Incidence	23.3%	70.2%	74.0%
Terminal Incidence	8/40 (20%)	25/39 (64%)	22/32 (69%)
Life Table	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Females			
Hepatocellular Carcinoma			
Overall Incidence	1/50 (2%)	6/50 (12%)	11/50 (22%)
Adjusted Incidence	2.5%	15.3%	28.8%
Terminal Incidence	1/40 (3%)	5/38 (13%)	10/37 (27%)
Life Table	P=0.001	P=0.053	P=0.002
Incidental Tumor Test	P=0.001	P=0.080	P=0.002
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.056	P=0.002
Hepatocellular Adenoma			
Overall Incidence	3/50 (6%)	9/50 (18%)	12/50 (24%)
Adjusted Incidence	7.5%	23.7%	31.4%
Terminal Incidence	3/40 (7%)	9/38 (24%)	11/37 (30%)
Life Table	P=0.006	P=0.049	P=0.008
Incidental Tumor Test	P=0.006	P=0.049	P=0.008
Cochran-Armitage Trend Test	P=0.010		
Fisher Exact Test		P=0.061	P=0.011

Adrenal: Pheochromocytomas of the adrenal gland were observed with a significant positive trend in male mice (Table 23). In pairwise comparisons between the control and dosed groups, the incidences were significant in both the low dose and the high dose groups. These neoplasms varied in size and compressed the cortical cells. Cells were arranged in cords or lobules and had granular basophilic cytoplasm. Nuclei had stippled or granular chromatin and a nucleolus. Mitotic figures were not numerous. In two mice, nests of tumor cells were in the adipose tissue around the adrenal glands. This tumor type was not observed in statistically significant proportions in female mice.

TABLE 23. INCIDENCES OF MALE MICE WITH PHEOCHROMOCYTOMAS OF THE ADRENAL GLAND

	Control	Low Dose	High Dose
Overall Incidence	2/48 (4%)	12/49 (24%)	14/49 (29%)
Adjusted Incidence	5.1%	29.8%	39.5%
Terminal Incidence	2/39 (5%)	11/39 (28%)	11/32 (34%)
Life Table	P<0.001	P=0.004	P<0.001
Incidental Tumor Test	P<0.001	P=0.006	P<0.001
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.004	P=0.001

Hematopoietic system: Malignant lymphoma occurred with a significant positive trend in female mice (Table 24). In pairwise comparisons with the control group, the incidences were significant for both the low dose and the high dose groups.

The liver, spleen, lymph nodes, and/or thymus were enlarged in mice with these lymphomas. Distribution of the neoplasms was fairly uniform and minimal organization was present. Cells were crowded in areas, and some cells had more cytoplasm than others. Nuclei were large, with stippled or coarse chromatin and one to two nucleoli. Mitotic figures were numerous. Histiocytes and necrotic material interspersed between these cells imparted a "starry-skied" appearance in one or two mice. Numerous multinucleate giant cells were present in the lymph nodes of one mouse. This tumor type was not observed in statistically significant proportions in male mice.

TABLE 24. INCIDENCES OF FEMALE MICE WITH MALIGNANT LYMPHOMA

	Control	Low Dose	High Dose
Overall Incidence	13/50 (26%)	28/50 (56%)	29/50 (58%)
Adjusted Incidence	31.7%	61.9%	64.3%
Terminal Incidence	12/40 (30%)	21/38 (55%)	21/37 (57%)
Life Table	P=0.001	P=0.002	P=0.001
Incidental Tumor Test	P=0.001	P=0.002	P=0.001
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		P=0.002	P=0.001

Lung: Alveolar/bronchiolar adenomas were observed with a significant positive trend in female mice (Table 25). In pairwise comparisons with the controls, the incidence in high dose groups was significant. The adenomas compressed the normal pulmonary parenchyma. Cells were arranged in acinar or tubular structures or grew as sheets. Cuboidal cells had an eosinophilic cytoplasm. Nuclei were hyperchromatic. The carcinomas involved part or an entire lobe of the lung. A pleomorphism in the size and shape of cells was apparent.

Emboli of cells were occasionally found in the bronchioles or in blood vessels. The incidence of male mice with alveolar/bronchiolar adenomas occurred with a significant negative trend, and in pairwise comparisons the incidence in high dose groups was significantly lower than that in the controls.

Kidney: Nonneoplastic lesions were observed at the incidences presented in Table 26. Degenerative changes in the renal cortical tubules ranged from loss of cytoplasmic basophilia to cell degeneration. Strands of lacy material were present in tubules in which there were no cells. Proteinaceous material, which was stained red with eosin, had filled the lumina of the tubules. In some glomeruli, there was an increased cellularity, and the mesangium and Bowman's capsule were thickened. Mineralization of the renal papilla was seen in the kidneys of some mice.

TABLE 25. INCIDENCES OF MICE WITH ALVEOLAR/BRONCHIOLAR ADENOMA

	Control	Low Dose	High Dose
Males			
Overall Incidence	12/49 (24%) *(a)*	9/49 (18%) *(b)*	3/49 (6%) *(a)*
Adjusted Incidence	29.1%	21.3%	9.4%
Terminal Incidence	11/40 (28%)	6/38 (16%)	3/32 (9%)
Life Table Test	P=0.031N	P=0.360N	P=0.035N
Incidental Tumor Test	P=0.017N	P=0.313N	P=0.030N
Cochran-Armitage Trend Test	P=0.010N		
Fisher Exact Test		P=0.312N	P=0.011N
Females			
Overall Incidence	1/50 (2%) *(a)*	2/50 (4%) *(a)*	6/49 (12%) *(c)*
Adjusted Incidence	2.5%	5.3%	16.7%
Terminal Incidence	1/40 (3%)	2/38 (5%)	6/36 (17%)
Life Table Test	P=0.021	P=0.482	P=0.042
Incidental Tumor Test	P=0.021	P=0.482	P=0.042
Cochran-Armitage Trend Test	P=0.027		
Fisher Exact Test		P=0.500	P=0.053

(a) One additional mouse had an alveolar/bronchiolar carcinoma.
(b) Four additional mice had alveolar/bronchiolar carcinomas.
(c) Two additional mice had alveolar/bronchiolar carcinomas.

TABLE 26. INCIDENCES OF MICE WITH NONNEOPLASTIC LESIONS OF THE KIDNEY

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Kidneys Evaluated	49	50	50	50	50	50
Nephropathy	18	34	36	6	21	35
Kidney Mineralization	24	28	10	2	8	8
Renal Papilla Mineralization	1	2	12	1	1	14

TABLE 27. INCIDENCES OF MICE WITH PRIMARY TUMORS THAT OCCURRED WITHOUT SIGNIFICANT GROUP DIFFERENCES *(a)*

	Control	Low Dose	High Dose
Males			
Adrenal: Adenoma	3/48 (6%)	1/49 (2%)	0/49 (0%)
Circulatory System:			
Hemangioma	3/49 (6%)	6/50 (12%)	4/50 (8%)
Angiosarcoma or Hemangiosarcoma	5/49 (10%)	3/50 (6%)	7/50 (14%)
Hemangioma, Angiosarcoma, or Hemangiosarcoma	7/49 (14%)	9/50 (18%)	8/50 (16%)
Hematopoietic System:			
Lymphoma, All Malignant	10/49 (20%)	9/50 (18%)	11/50 (22%)
Liver: Hepatocellular Adenoma	7/49 (14%)	10/50 (20%)	8/50 (16%)
Lung: Alveolar/Bronchiolar Carcinoma	1/49 (2%)	4/49 (8%)	1/49 (2%)
Subcutaneous Tissue: Sarcoma	4/49 (8%)	1/50 (2%) *(b)*	2/50 (4%)
Females			
Circulatory System:			
Angiosarcoma	1/50 (2%)	1/50 (2%)	4/50 (8%)
Hemangioma	2/50 (4%)	1/50 (2%)	3/50 (6%)
Angiosarcoma or Hemangiosarcoma	1/50 (2%)	2/50 (4%)	4/50 (8%)
Hemangioma, Angiosarcoma, or Hemangiosarcoma	3/50 (6%)	3/50 (6%)	6/50 (12%)
Ovary: Tubular Adenoma	2/43 (5%)	3/38 (8%)	0/34 (0%)
Pituitary: Adenoma	12/42 (29%)	8/40 (20%)	14/39 (36%)
Stomach: Papillomatosis	3/50 (6%)	1/49 (2%)	0/48 (0%)
Subcutaneous Tissue: Sarcoma	2/50 (4%)	3/50 (6%)	0/50 (0%)

(a) Primary tumors that occurred at an incidence of at least 5% but were not significant by statistical analyses.
(b) One animal had a neurofibrosarcoma.

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Carcinogenesis studies of 4,4'-methylenedianiline dihydrochloride were conducted by administering this chemical in the drinking water of F344/N rats and B6C3F$_1$ mice. Groups of 50 rats and 50 mice of each sex received drinking water containing 150 or 300 ppm 4,4'-methylenedianiline dihydrochloride (dosage expressed as the free base; purity greater than 98%) for 103 weeks. Groups of 50 rats and 50 mice of each sex, given drinking water adjusted with 0.1N HCl to the pH (3.7) of the 300-ppm formulation, served as controls.

4,4'-Methylenedianiline is an aromatic amine structurally similar to a number of carcinogenic compounds (Table 28). The potential for human exposure to 4,4'-methylenedianiline at levels sufficient to cause serious injury has been demonstrated by both accidental (Kopelman et al., 1966) and industrial (McGill and Motto, 1974) exposures. The route of exposure was oral (contaminated bread) in the accidental cases and probably dermal or oral in the industrial incidents, although inhalation was not absolutely ruled out (McGill and Motto, 1974). 4,4'-Methylenedianiline is now generally used in closed system manufacture of epoxy resins. The potential for 4,4'-methylenedianiline exposure via cured epoxy resin products has not been thoroughly addressed, and exposure estimates are not readily available.

4,4'-Methylenedianiline's mutagenic activity has been compared specifically with that of other aromatic amines (Lavoie et al., 1979; Rao et al., 1982), antithyroid agents and thyroid carcinogens (Spencer and Hosain, 1980), and carcinogenic aromatic amines (Miller, 1978). 4,4'-Methylenedianiline has been included in structure/activity studies in which the atoms linking the aniline moieties were varied (Lavoie et al., 1979) and the chemical analogs were tested in *Salmonella typhimurium* TA98 and TA100. After metabolic activation, 4,4'-oxydianiline (ether linkage, Table 28) and thiodianiline (sulfide linkage, Table 28) were two and four times more mutagenic than 4,4'-methylenedianiline, and 4,4'-methylenedianiline was more mutagenic than 4-aminophenyl disulfide (disulfide linkage). Substitution of functional groups ortho to the amino groups could alter 4,4'-methylenedianiline's mutagenicity (Rao et al., 1982), but substitution with alkyl or alkoxycarbonyl groups did not affect or reduce 4,4'-methylenedianiline mutagenicity in TA98. However, the substitution with chlorine or fluorine enhanced mutagenicity.

The Bioassay Program has studied certain aromatic amines which are structurally related to 4,4'-methylenedianiline (Table 28). Michler's ketone was the only compound listed which did not significantly increase tumors in the thyroid in either of the species studied. All of the compounds listed in Table 28 did cause cancer of the liver in either mice or rats. In the current studies, 4,4'-methylenedianiline dihydrochloride (4,4'-methylenedianiline • 2HCl) exposure increased liver and thyroid tumors in both species. The carcinogenic activity of 4,4'-methylenedianiline • 2HCl was attributed to the parent compound 4,4'-methylenedianiline. The dihydrochloride is more stable and soluble than 4,4'-methylenedianiline and was chosen to facilitate the preparation of dosage solutions, and to administer the chemical by drinking water.

The administration of antithyroid drugs to rats or mice has been associated with enlargement of the thyroid gland and development of benign and malignant thyroid tumors (Dalton et al., 1945; Griesbach et al., 1945; Seifter et al., 1949). The effect of 4,4'-methylenedianiline on the thyroid is particularly interesting in this study. 4,4'-Methylenedianiline and the compounds listed in Table 28 certainly bear a significant structural resemblance to triiodothyronine (T_3) (Figure 5) and thyroxine (T_4). These compounds possess many of the chemical features

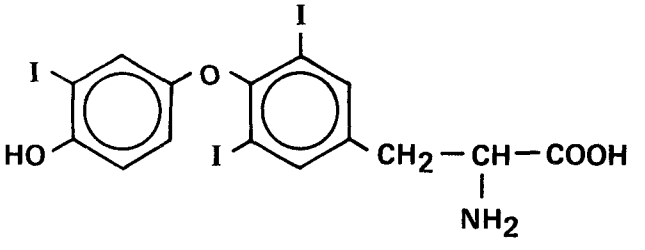


Figure 5. Structure of Triiodothyronine

seen in T_3 analogs which bind to nuclear receptor sites and mimic thyroid hormone biologic activity (Oppenheimer, 1979). It has been hypothesized that, for biological activity, the antithyroid compounds are iodinated via thyroid peroxidase (Spencer and Hosain, 1980). The same mechanism of action for thyroid carcinogens, such as 2,4-diaminoanisole (NCI, 1978b and Ward et al., 1979) and 4,4'-methylenedianiline, has been proposed but not tested (Spencer and Hosain, 1980).

Since 4,4'-methylenedianiline has been demonstrated to be mutagenic after metabolic activation (Darby et al., 1978; Andersen et al., 1980), 4,4'-methylenedianiline's thyroid carcinogenic activity may involve a genetic mechanism of action. There is also a potential nongenetic mechanism of carcinogenesis involving thyroid hormone activity or inhibition. The nongenetic theory finds support in the goitrogenic activity of 4,4'-methylenedianiline demonstrated in the subchronic phase of this study. Yet another possible explanation of 4,4'-methylenedianiline's thyroid carcinogenicity is that, while 4,4'-methylenedianiline ultimately may act via a genetic mechanism, it could have special affinity for the thyroid and bind to the hormone receptor. The relationship of the thyroid hormone receptor to 4,4'-methylenedianiline's thyroid carcinogenicity is as yet untested and beyond the scope of this study. Although 4,4'-methylenedianiline and structurally similar compounds may share a common mechanism of carcinogenic action, the various theories concerning the mode of action are unproven.

4,4'-Methylenedianiline is hepatotoxic in humans (Kopelman et al., 1966; McGill and Motto, 1974) and animals (Diechmann et al., 1978; IARC, 1974a), and 4,4'-methylenedianiline and similar aromatic amines are mutagenic after metabolic activation by liver microsomes (Lavoie et al., 1979). The metabolic activation of 4,4'-methylenedianiline to a reactive electrophile may be responsible for a number of nonneoplastic lesions in this study. Both the liver and kidney have significant levels of the enzymes necessary for the metabolic activation of 4,4'-methylenedianiline. The liver (sinusoidal) dilatation in male rats, fatty metamorphosis and focal cellular change in male and female rats, liver degeneration in male mice, kidney mineralization in male rats, and renal papillary mineralization in male and female mice may all be due to the local formation of a common toxic metabolite.

The hepatocarcinogenic activity of these compounds may also require metabolic activation to electrophilic metabolites which bind DNA (Miller, 1978). However, the hepatocarcinogenic activity may be secondary to hepatotoxicity and may occur via a nongenetic mechanism. Several criteria were developed to predict the carcinogenic activity of 4,4'-methylenedianiline and similar compounds (Thuraisingham and Nilar, 1980). This model predicted that 4,4'-methylenedianiline and other chemicals such as 4,4'-methylene bis(2-methylaniline) and 4,4'-methylene bis(2-chloroaniline) would be carcinogenic (IARC, 1974a; Thuraisingham and Nilar, 1980); the latter two compounds differ from 4,4'-methylenedianiline by the substitution of methyl groups or chlorine ortho to the NH_2 groups. According to theory, a stable ArNH+ electrophile may be H+ formed from 4,4'-methylenedianiline and from similar compounds; however, the metabolic pathways for 4,4'-methylenedianiline are not known.

IARC (1974a) has determined that previous tests of 4,4'-methylenedianiline's carcinogenicity were inconclusive. A more recent study on the feeding of 4,4'-methylenedianiline to dogs indicated that 4,4'-methylenedianiline did not produce tumors of the urinary bladder or liver. However, that study contained only nine dogs and no control animals; only three animals survived for 7 years and the thyroid was not studied in any of the dogs (Diechmann et al., 1978). In a study where 4,4'-methylenedianiline was fed to rats for up to 40 weeks, intrahepatic bile duct proliferation was induced (Fukushima et al., 1979). Bile duct hyperplasia was increased in a dose-related manner in the current 2-year studies for male and female rats (Tables C1 and C2). In the current 13-week studies, bile duct hyperplasia was observed in all male and female rats that received 800 ppm 4,4'-methylenedianiline, in 4/10 male and 3/10 female rats that received 400 ppm 4,4'-methylenedianiline, and in 5/10 male and 4/10 female mice that received 400 ppm 4,4'-methylenedianiline; it was not detected in control animals. Although only one bile duct adenoma occurred in a 300 ppm male rat in the 2-year study, it may be biologically significant because of the dose-related incidences of bile duct hyperplasia in rats and the absence of bile duct adenomas in historical control male rats 0/3,633. Hence, the statement by Fukushima et al. (1979) that "proliferation of bile ductular cells induced by [4,4'-methylenedianiline] is . . . unrelated to neoplasia" may not be correct.

IV. DISCUSSION AND CONCLUSIONS

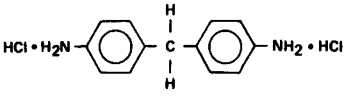
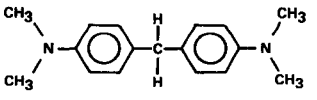
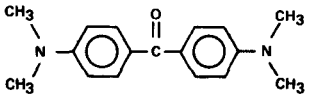
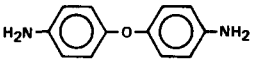
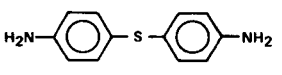
Rubino et al. (1982) have reported epidemiological evidence that appears to associate *o*-toluidine and 4,4'-methylene bis(2-methylaniline) with an increased risk of bladder cancer. The cohort comprises workers in a dyestuff factory in Northern Italy. These authors record five deaths from bladder cancer versus the expected 0.08 for workers engaged in manufacturing fuchsin and safranine T. Rubino et al. (1982) conclude that the precursors for these products [*o*-toluidine and 4,4'-methylene bis(2-methylaniline)] "should be regarded as almost certainly capable of causing cancer of the bladder in man." Further, mortality from bladder cancer was much higher among those exposed to benzidine and naphthylamines manufacture as compared to those exposed only in use or intermittent contact; these cases are distinct from those mentioned above. In the 2-year carcinogenesis studies, three dosed female rats had transitional cell papillomas of the urinary bladder.

In addition, several rare tumors (bile duct adenoma in male rats and ovarian granulosa cell tumors and urinary bladder transitional cell papillomas in female rats) may have been related to administration of 4,4'-methylenedianiline dihydrochloride. Incidences of alveolar/bronchiolar adenomas of the lung were increased in female mice; the same tumor in male mice occurred with a negative trend. The reason for the significant decrease in leukemia for dosed male rats is unknown.

Neither the reason for nor the impact of a dose-related reduction in water consumption in both male and female rats are known.

Conclusions: Under the conditions of these studies 4,4'-methylenedianiline dihydrochloride was carcinogenic for F344/N rats and B6C3F$_1$ mice of each sex, causing significantly increased incidences of thyroid follicular cell carcinomas in male rats, thyroid follicular cell adenomas in female rats and in mice of each sex, C-cell adenomas of the thyroid gland in female rats, neoplastic nodules in the liver of male rats, hepatocellular carcinomas in mice of each sex, adenomas of the liver and malignant lymphomas in female mice, and adrenal pheochromocytomas in male mice.

TABLE 28. COMPARISON OF RESULTS OF CHRONIC NCI/NTP STUDIES ON 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE AND RELATED COMPOUNDS

Test Substance	Structure	Species	Sex	Dose (ppm)	Site of Neoplastic Lesion Observed	
					Liver	Thyroid
4,4'-Methylenedianiline dihydrochloride (Current Study)		Rat	M	300 *(a)*	N *(b)*	N
		(F344)	F	300		N
		Mouse	M	300	N	N
		(B6C3F$_1$)	F	300	N	N
4,4'-Methylenebis (N,N-dimethyl) benzenamine (NCI 1978)		Rat	M	750 *(c)*		N
		(F344)	F	750		N
		Mouse	M	2,500		
		(B6C3F$_1$)	F	2,500	N	
Michler's Ketone (NCI, 1978a)		Rat	M	500 *(c)*	N	
		(F344)	F	1,000	N	
		Mouse	M	2,500		
		(B6C3F$_1$)	F	2,500	N	
4,4'-Oxydianiline (NCI, 1981)		Rat	M	500 *(c)*	N	N
		(F344)	F	500	N	N
		Mouse	M	800		
		(B6C3F$_1$)	F	800	N	N
4,4'-Thiodianiline (NCI, 1978c)		Rat	M	3,000 *(c)*	N	N
		(F344)	F	3,000		N
		Mouse	M	5,000	N	N
		(B6C3F$_1$)	F	5,000	N	N

(a) In drinking water

(b) N = Neoplastic lesion occurred at statistically significant incidence ($P<0.025$ by the Fisher exact test)

(c) In feed

V. REFERENCES

V. REFERENCES

Andersen, M.; Binderup, M.-L.; Kiel, P.; Larsen, H.; Maxlid, J., Mutagenic action of isocyanates used in the production of polyurethanes. Scand. J. Work. Environ. Health; 6:221-226; 1980.

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

Beilstein Handbuck der Organischen Chemis, Verlag von Julius Springer, 13; 1918:238.

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

Calder, I.; Williams, P.; Funder, C.; Green, C.; Ham, K.; Tange, J., Nephrotoxicity and hepatotoxicity from substituted anilines. Nephron 10(6):361; 1973.

Cox, D.R., Regression models and life tables. J.R. Stat. Soc. B34; 187-220; 1972.

Dalton, A.J.; Morris, H.P.; Dubnik, C.S., Morphologic changes in the organs of female C3H mice after long-term ingestion of thiourea and thiouracil. J. Natl. Cancer Inst. 9:201-223; 1945.

Darby, T.; Johnson, H.; Northup, S., An evaluation of a polyurethane for use as a medical-grade plastic. Toxicol. Appl. Pharmacol. 46:449-453; 1978.

Deichmann, W.B.; MacDonald, W.E.; Coplan, M.; Woods, F.; Blum, E., Di(4-aminophenyl)-methane (MDA): 4-7 year dog feeding study. Toxicology 11:185-188; 1978.

Fukushima, S.; Shibata, M.; Hibino, T.; Yoshimura, T.; Horose, M.; Ito, N., Intrahepatic bile duct proliferation induced by 4,4'-diaminodiphenylmethane in rats. Toxicol. Appl. Pharmacol. 48:145-155; 1979.

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

Golke, R., 4,4-Diaminodiphenylmethan im chronischen versuch. Z. Gesamte Hyg. Ihre Grenzgeb. 24(3):159-162; 1978.

Griesbach, W.E.; Kennedy, T.H.; Purves, H.D., Studies on experimental goitre. VI. Thyroid adenomata in rats on *Brassica* seed diet. Br. J. Exp. Pathol., 26:18-24, 1945.

IARC, Benzidine. In: IARC monographs on the evaluation of carcinogenic risk of chemicals to humans. Vol 29, Geneva: World Health Organization, 1982:149-183.

IARC, 4,4'-Methylene bis(2-chloraniline). In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to man: some aromatic amines, hydrazine and related substances, N-nitroso compounds and miscellaneous alkylating agents, Vol. 4, Geneva: World Health Organization, 1974a:65.

IARC, 4,4'-Methylenedianiline. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to man: some aromatic amines, hydrazine and related substances, N-nitroso compounds and miscellaneous alkylating agents, Vol. 4, Geneva: World Health Organization, 1974b:79.

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

Kirk-Othmer, Encyclopedia of chemical technology, 2nd ed. New York: Intersciences Publishers, 2:414, 418; 1963; 8:311; 1965.

Kopelman, H.; Robertson, M.H.; Sanders, P.G.; Ash, I., The Epping jaundice. Brit. Med. J. 1:514-516; 1966.

Lavoie, E.; Tulley, L.; Fow, E.; Hoffmann, D., Mutagenicity of aminophenyl and nitrophenyl ethers, sulfides, and disulfides. Mutat. Res. 67:123-131; 1979.

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

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

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

McGill, D.; Motto, J., An industrial outbreak of toxic hepatitis due to methylenedianiline. New Eng. J. Med. 291(6):278-282; 1974.

Merck Index, 9th ed. Rahway, NJ: Merck and Company; 1976:2943.

Miller, E.C.; Some current perspectives on chemical carcinogenesis in humans and experimental animals: presidential address. Cancer Res. 38:1479-1496; 1978.

Munn, A., in Bladder Cancer, Chap. 16, Deichmann, W.; Lampe, K., ed. Birmingham, Alabama, 1967:187-193.

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

V. REFERENCES

NCI, National Cancer Institute, Bioassay of 4,4'-methylenebis(N,N-dimethyl)-benzene-amine for possible carcinogenicity, NCI TR 186, Department of Health, Education, and Welfare, Bethesda, Maryland, 1978.

NCI, National Cancer Institute, Bioassay of Michler's Ketone for possible carcinogenicity, NCI TR 181, Department of Health, Education, and Welfare, Bethesda, Maryland, 1978a.

NCI, National Cancer Institute, Bioassay of 2,4-diaminoanisole sulfate for possible carcinogenicity, NCI TR 84, Department of Health, Education and Welfare, Bethesda, Maryland, 1978b.

NCI, National Cancer Institute, Bioassay of 4,4'-thiodianiline for possible carcinogenicity, NCI TR 47, Department of Health, Education, and Welfare, Bethesda, Maryland, 1978c.

NCI, National Cancer Institute, Bioassay of 4,4'-oxydianiline for possible carcinogenicity, TR 205, Department of Health and Human Services, Bethesda, Maryland, 1981.

NIOSH, National Institute for Occupational Safety and Health, 4,4-Diaminodiphenylmethane (DDM), Current Intelligence Bulletin 8, 1976.

Oppenheimer, J.H., Thyroid hormone action at the cellular level. Sci. 203:971, 1979.

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

Pludro, G.; Karlowski, K.; Mankowska, M.; Woggon, H.; Uhde, W.-J., Toxicological and chemical studies of some epoxy resins and hardeners. Acta Polon. Pharm. 26(4):352, 1969.

Rao, T.K.; Dorsey, G.F.; Allen, B.E.; Epler, J.L., Mutagenicity of 4,4'-methylenedianiline derivatives in the *Salmonella* histidine reversion assay. Arch. Toxicol. 49:185-190, 1982.

Rubino, G.F.; Scansetti, G.; Piolatto, G.; Pira, E., The carcinogenic effect of aromatic amines: an epidemiological study on the role of *o*-toluidine and 4,4'-methylene bis(2-methylaniline) in inducing bladder cancer in man. Environ. Res. 27:241-254, 1982.

Sadtler Research Laboratories. Sadtler standard spectra. Philadelphia: Sadtler Research Laboratories; IR No. 42877, UV No. 19954, NMR No. 1457.

Seifter, J.; Ehrick, W.E.; Hudyma, G.M., Effects of prolonged administration of antithyroid compounds on the thyroid and other endocrine organs of the rat. Arch. Pathol. 48:536-547; 1949.

Shimizu, H.; Takemura, N., Mutagenicity and carcinogenicity of some aromatic amino and nitro compounds. Jap. J. Ind. Health 18:138-139; 1976.

Spencer, R.P.; Hosain, H., Thionamides and analogues: a reappraisal of antithyroid and thyroid carcinogenic effects. Med. Hypotheses 6:199-205; 1980.

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

Steinhoff, D.; Grundmann, E., Zur cancerogenen Wirkung von 4,4'-Diaminodiphenylmethan und 2,4'-Diaminodiphenylmethan. Naturwissenschaften 57(5):247-248; 1970.

Takemura, N., Shimizu, H., Mutagenicity of some aromatic amino- and nitro-compounds. Mutat. Res. 54(2):256; 1978.

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

Thuraisingham, R.A.; Nilar, S.H.M., A theoretical study of the carcinogenic nature of some aromatic amines. J. Theor. Biol. 86:577-580; 1980.

Tullner, W., Endocrine effects of methylenedianiline in the rat, rabbit and dog. Endocrinology 66:470-474; 1960.

USCFR, U.S. Code of Federal Regulations, 21:175-300; 1977.

Ward, J.M.; Stinson, S.F.; Hardisty, J.F.; Cockrell, B.Y.; Hayden, D.W., Neoplasms and pigmentation of thyroid glands in F344 rats exposed to 2,4-diaminoanisole sulfate, a hair dye component, J. Natl. Canc. Inst. 62:1067-1073; 1979.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

	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		4 (8%)	1 (2%)
SQUAMOUS CELL CARCINOMA	1 (2%)		
BASAL-CELL CARCINOMA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
FIBROMA	5 (10%)	1 (2%)	2 (4%)
FIBROSARCOMA		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
NEOPLASM, NOS, METASTATIC	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	3 (6%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
PHEOCHROMOCYTOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
LEUKEMIA,NOS	1 (2%)		
MYELOMONOCYTIC LEUKEMIA	9 (18%)	6 (12%)	5 (10%)
*HEMATOPOIETIC SYSTEM	(50)	(50)	(50)
LEUKEMIA,NOS	2 (4%)		
#SPLEEN	(49)	(50)	(49)
SARCOMA, NOS			1 (2%)
#THYMUS	(40)	(39)	(37)
THYMOMA	1 (3%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*ADIPOSE TISSUE	(50)	(50)	(50)
HEMANGIOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
BILE DUCT ADENOMA			1 (2%)
NEOPLASTIC NODULE	1 (2%)	12 (24%)	25 (50%)
HEPATOCELLULAR CARCINOMA		1 (2%)	1 (2%)
#PANCREAS	(49)	(49)	(47)
ACINAR-CELL ADENOMA	1 (2%)		1 (2%)
#STOMACH	(49)	(50)	(49)
NEUROFIBROSARCOMA	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(47)	(49)
CARCINOMA,NOS	1 (2%)	2 (4%)	1 (2%)
ADENOMA, NOS	24 (52%)	20 (43%)	21 (43%)
#ADRENAL	(50)	(49)	(49)
PHEOCHROMOCYTOMA	7 (14%)	5 (10%)	5 (10%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)		
#THYROID	(49)	(47)	(48)
FOLLICULAR-CELL ADENOMA	1 (2%)	4 (9%)	3 (6%)
FOLLICULAR-CELL CARCINOMA			7 (15%)
C-CELL ADENOMA	1 (2%)	2 (4%)	1 (2%)
C-CELL CARCINOMA	2 (4%)		1 (2%)
#PARATHYROID	(17)	(16)	(14)
ADENOMA, NOS	1 (6%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC ISLETS	(49)	(49)	(47)
ISLET-CELL ADENOMA	2 (4%)	4 (8%)	3 (6%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
FIBROADENOMA	2 (4%)	1 (2%)	2 (4%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		2 (4%)
ADENOMA, NOS	3 (6%)		1 (2%)
#TESTIS	(49)	(50)	(50)
INTERSTITIAL-CELL TUMOR	42 (86%)	42 (84%)	47 (94%)
INTERSTITIAL-CELL TUMOR, MALIGNA			1 (2%)
*EPIDIDYMIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR, INVASIV			1 (2%)
*VAS DEFERENS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR, INVASIV			1 (2%)
*SCROTUM	(50)	(50)	(50)
LEIOMYOSARCOMA		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(49)
ASTROCYTOMA		1 (2%)	
SPECIAL SENSE ORGANS			
*EAR	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
LIPOSARCOMA			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	6	6
MORIBUND SACRIFICE	5	4	4
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	37	40	40
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	50	50	49
TOTAL PRIMARY TUMORS	115	117	139
TOTAL ANIMALS WITH BENIGN TUMORS	49	48	48
TOTAL BENIGN TUMORS	93	88	92
TOTAL ANIMALS WITH MALIGNANT TUMORS	19	15	17
TOTAL MALIGNANT TUMORS	21	16	22
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		1
TOTAL SECONDARY TUMORS	2		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	13	25
TOTAL UNCERTAIN TUMORS	1	13	25
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 ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

	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			2 (4%)
BASAL-CELL CARCINOMA	1 (2%)		
SARCOMA, NOS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS			2 (4%)
FIBROMA	1 (2%)		
FIBROSARCOMA	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
BASAL-CELL CARCINOMA, INVASIVE	1 (2%)		
ADENOCARCINOMA, NOS, METASTATIC		2 (4%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
C-CELL CARCINOMA, METASTATIC		1 (2%)	
SARCOMA, NOS, METASTATIC	1 (2%)		
FIBROSARCOMA, METASTATIC			1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MYELOMONOCYTIC LEUKEMIA	3 (6%)	7 (14%)	2 (4%)
#SPLEEN	(49)	(50)	(50)
GRANULOSA-CELL CARCINOMA, INVASI		1 (2%)	
#THYMUS	(38)	(42)	(41)
THYMOMA			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	4 (8%)	8 (16%)	8 (16%)
URINARY SYSTEM			
#URINARY BLADDER	(48)	(50)	(50)
TRANSITIONAL-CELL PAPILLOMA		2 (4%)	1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(49)	(49)
CARCINOMA,NOS		2 (4%)	3 (6%)
ADENOMA, NOS	31 (63%)	25 (51%)	34 (69%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)		2 (4%)
PHEOCHROMOCYTOMA	1 (2%)	2 (4%)	1 (2%)
GANGLIONEUROMA			1 (2%)
#THYROID	(47)	(47)	(48)
FOLLICULAR-CELL ADENOMA		2 (4%)	17 (35%)
FOLLICULAR-CELL CARCINOMA		2 (4%)	2 (4%)
C-CELL ADENOMA		3 (6%)	6 (13%)
C-CELL CARCINOMA	1 (2%)	2 (4%)	1 (2%)
#PANCREATIC ISLETS	(47)	(48)	(49)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS	4 (8%)	4 (8%)	
FIBROADENOMA	10 (20%)	14 (28%)	9 (18%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS	2 (4%)	4 (8%)	5 (10%)
#UTERUS	(48)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
PAPILLARY ADENOCARCINOMA	1 (2%)		
SARCOMA, NOS		1 (2%)	
ENDOMETRIAL STROMAL POLYP	11 (23%)	15 (30%)	12 (24%)
ENDOMETRIAL STROMAL SARCOMA	3 (6%)		1 (2%)
#OVARY	(50)	(50)	(50)
GRANULOSA-CELL TUMOR		3 (6%)	2 (4%)
GRANULOSA-CELL CARCINOMA		1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
ASTROCYTOMA	1 (2%)	2 (4%)	2 (4%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	9	7	3
MORIBUND SACRIFICE	3	8	4
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	38	35	43
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	43	48	49
TOTAL PRIMARY TUMORS	80	101	118
TOTAL ANIMALS WITH BENIGN TUMORS	37	45	48
TOTAL BENIGN TUMORS	58	68	92
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	20	14
TOTAL MALIGNANT TUMORS	18	22	16
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	4	1
TOTAL SECONDARY TUMORS	2	4	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	4	10	9
TOTAL UNCERTAIN TUMORS	4	11	10
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 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	096	105	086	105	105	082	094	105	105	105	105	105	094	106	106	105	105	095	095	097	106	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA							X		X											X					
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASM, NOS, METASTATIC																					X				
ALVEOLAR/BRONCHIOLAR ADENOMA																									
PHEOCHROMOCYTOMA, METASTATIC																								X	
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
THYMUS	+	-	-	+	+	+	+	-	-	+	+	+	+	+	-	+	+	+	+	-	+	-	+	-	+
THYMOMA																					X				
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
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													X												
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-
STOMACH	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEUROFIBROSARCOMA																					X				
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																						X			
ADENOMA, NOS		X		X	X		X			X	X	X		X		X	X						X	X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA	X															X							X	X	
PHEOCHROMOCYTOMA, MALIGNANT																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA	X																								
C-CELL ADENOMA																							X		
C-CELL CARCINOMA													X												
PARATHYROID	-	-	+	-	→	+	-	+	-	-	-	+	+	-	-	-	-	+	-	-	+	-	-	-	-
ADENOMA, NOS																									
PANCREATIC ISLETS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA			X																						
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	+	+	N	N	N	N	+	N	N	+	N	N	N	+	N	N	N	N	N	+	N
ADENOMA, NOS											X														
FIBROADENOMA					X	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
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
CARCINOMA,NOS																									
ADENOMA, NOS																				X					X
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																								X	
BODY CAVITIES																									
PERITONEUM	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																									
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																									
MYELOMONOCYTIC LEUKEMIA		X			X											X								X	
HEMATOPOIETIC SYSTEM																									
LEUKEMIA,NOS			X					X																	

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

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

ANIMAL NUMBER	02 56	02 67	02 68	02 69	03 01	03 11	03 12	03 33	03 34	03 51	03 56	03 57	03 58	03 59	04 01	04 11	04 12	04 33	04 41	04 51	04 56	04 57	04 58	04 59	05 00	TOTAL
WEEKS ON STUDY	105	106	106	104	105	106	106	106	057	086	086	093	106	095	105	106	106	104	106	106	106	090	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA																		X								1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA			X																		X					5
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASM, NOS, METASTATIC																										1
ALVEOLAR/BRONCHIOLAR ADENOMA					X																					2
PHEOCHROMOCYTOMA, METASTATIC		X																								1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	40
THYMOMA																										1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																			X							1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ACINAR-CELL ADENOMA																										1
ESOPHAGUS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NEUROFIBROSARCOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	46
CARCINOMA,NOS																										1
ADENOMA, NOS	X	X	X			X	X	X	X					X			X			X	X	X				25
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA								X					X							X					7
PHEOCHROMOCYTOMA, MALIGNANT		X																								1
THYROID	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																										1
C-CELL ADENOMA																										1
C-CELL CARCINOMA																	X									2
PARATHYROID	+	+	+	-	-	+	-	+	-	+	+	-	-	-	-	-	+	+	-	-	-	-	-	+	-	17
ADENOMA, NOS																								X		1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																									X	2
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	50
ADENOMA, NOS																										1
FIBROADENOMA																										2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X		X	X	X	42
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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
CARCINOMA,NOS				X																						1
ADENOMA, NOS														X												3
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SARCOMA, NOS																										1
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	X	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	N	N	50
LEUKEMIA,NOS																										1
MYELOMONOCYTIC LEUKEMIA										X			X					X				X		X		9
HEMATOPOIETIC SYSTEM																										
LEUKEMIA,NOS																										2

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

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	082	105	105	105	105	105	105	061	105	105	105	105	105	105	103	099	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA												X				X				X					
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROMA																									
FIBROSARCOMA										X															
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA						X					X	X													
ALVEOLAR/BRONCHIOLAR CARCINOMA												X													
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	-	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE				X									X				X						X		X
HEPATOCELLULAR CARCINOMA																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA												X													
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	
CARCINOMA,NOS																			X						
ADENOMA, NOS		X	X			X	X					X		X				X			X				
ADRENAL	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA									X			X							X		X				
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA									X																X
C-CELL ADENOMA																									
PARATHYROID	-	-	-	+	-	+	-	-	+	-	+	+	+	+	-	-	-	-	-	+	-	-	+	-	
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	
ISLET-CELL ADENOMA															X										
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	+	N	N	+	N	N	+	N
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
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA																									
BODY CAVITIES																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS										X															
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MYELOMONOCYTIC LEUKEMIA				X				X												X				X	
ADIPOSE TISSUE																	X								
HEMANGIOMA																									
SCROTUM NOS																									
LEIOMYOSARCOMA																									

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

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) 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	057	105	094	001	091	105	105	101	051	093	105	105	105	105	105	105	105	105	105	105	089	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA								X																		4
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																		X								1
FIBROMA							X																			1
FIBROSARCOMA					X																					2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										3
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+		48
THYMUS	-	+	+	-	-	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+		39
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE								X		X						X		X	X				X		X	12
HEPATOCELLULAR CARCINOMA							X																			1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+		48
LARGE INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CARCINOMA,NOS												X														2
ADENOMA, NOS			X			X	X	X			X		X		X	X	X	X		X		X				20
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA																		X								5
THYROID	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+		47
FOLLICULAR-CELL ADENOMA											X	X	X													4
C-CELL ADENOMA									X															X		2
PARATHYROID	-	+	-	-	-	-	-	-	+	+	-	-	+	-	-	+	+	-	-	-	-	-	-	-	-	16
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA						X			X																X	4
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	+	+	N	+	N	N	+	N	N	N	N	N	+	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		42
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA				X																						1
BODY CAVITIES																										
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MESOTHELIOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
MALIG LYMPHOMA, HISTIOCYTIC TYPE																								X		1
MYELOMONOCYTIC LEUKEMIA								X										X								6
ADIPOSE TISSUE																										
HEMANGIOMA																										1
SCROTUM NOS																										
LEIOMYOSARCOMA																	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 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

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	093	105	105	105	105	058	080	105	105	048	105	105	105	105	105	105	105	105	105	105	105	105	094	105	101
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA											X														
BASAL-CELL CARCINOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA									X																
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA					X																				
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
SARCOMA, NOS																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
THYMUS	-	+	+	+	+	+	+	+	+	-	+	+	-	+	-	-	+	+	+	+	+	+	-	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT ADENOMA																									
NEOPLASTIC NODULE		X	X		X		X	X			X	X					X	X	X	X		X	X		X
HEPATOCELLULAR CARCINOMA																									
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																						X			
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
CARCINOMA,NOS																									
ADENOMA, NOS	X		X	X				X	X	X	X			X		X						X		X	X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
PHEOCHROMOCYTOMA									X		X								X						
THYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
FOLLICULAR-CELL ADENOMA							X										X								
FOLLICULAR-CELL CARCINOMA					X										X							X			
C-CELL ADENOMA																									
C-CELL CARCINOMA			X																						
PARATHYROID	-	+	-	-	-	+	-	-	-	+	-	-	-	-	+	+	-	+	-	-	-	-	-	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
ISLET-CELL ADENOMA	X		X				X																		
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	+	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N	N	N	
FIBROADENOMA																									
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INTERSTITIAL-CELL TUMOR, MALIGNAN																									
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
CARCINOMA,NOS							X																		
ADENOMA, NOS																									
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
INTERSTITIAL-CELL TUMOR, INVASIVE																									
VAS DEFERNES, SPERMATIC CORD	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
INTERSTITIAL-CELL TUMOR, INVASIVE																									
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
LIPOSARCOMA																									
MYELOMONOCYTIC LEUKEMIA																		X							

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	104	104	103	105	103	103	103	105	105	105	105	105	105	105	105	105	103	105	103	103	105	105	104	102	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL PAPILLOMA																										1
BASAL-CELL CARCINOMA																			X							1
SUBCUTANEOUS TISSUE	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROMA																			X							2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA		X															X		X							4
ALVEOLAR/BRONCHIOLAR CARCINOMA									X																	1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SARCOMA, NOS																								X		1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+		46
THYMUS	+	-	+	+	-	+	-	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	-	37
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT ADENOMA														X												1
NEOPLASTIC NODULE				X		X	X				X			X	X	X	X	X	X					X		25
HEPATOCELLULAR CARCINOMA																	X									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
ACINAR-CELL ADENOMA																										1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA,NOS																	X									1
ADENOMA, NOS				X			X	X					X	X	X	X		X							X	21
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA														X					X							5
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	48
FOLLICULAR-CELL ADENOMA																		X								3
FOLLICULAR-CELL CARCINOMA			X			X			X									X		X						7
C-CELL ADENOMA																										1
C-CELL CARCINOMA																										1
PARATHYROID	-	-	+	+	+	-	-	-	-	-	-	-	-	-	+	-	-	+	+	+	-	-	-	-	+	14
PANCREATIC ISLETS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
ISLET-CELL ADENOMA																										3
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	+	N	N	N	N	N	N	N	+	N	+	N	N	N	N	N	+	+	N	N	N	N	N	N	50M
FIBROADENOMA												X							X							2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	47
INTERSTITIAL-CELL TUMOR, MALIGNAN					X																					1
PROSTATE	+	+	+	-	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	44
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
CARCINOMA,NOS																								X		2
ADENOMA, NOS													X													1
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	50M
INTERSTITIAL-CELL TUMOR, INVASIVE					X																					1
VAS DEFERNES, SPERMATIC CORD	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
INTERSTITIAL-CELL TUMOR, INVASIVE					X																					1
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	50M
LIPOSARCOMA							X																			1
MYELOMONOCYTIC LEUKEMIA		X												X			X							X		5

M ANIMALS NECROPSIED

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

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

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	106	106	107	105	106	106	106	106	106	106	093	103	106	078	102	104	092	106	106	104	106	106	106	056	106
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA																									
SARCOMA, NOS																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA						X																			
FIBROSARCOMA																	X								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA, INVASIVE																									
ALVEOLAR/BRONCHIOLAR ADENOMA																									X
SARCOMA, NOS, METASTATIC																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
SPLEEN	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	-	+	+	+	+	+	+	+	-	-	+	-	+	-	-	-	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE									X																
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
ESOPHAGUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS	X			X		X		X	X		X	X	X		X			X		X	X	X			X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA									X																
THYROID	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
C-CELL CARCINOMA																									
PARATHYROID	+	+	-	+	-	+	-	+	-	+	-	+	-	+	+	+	-	-	-	+	-	-	+	+	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	N	N	N	N	N	N	N	N	N	+	+	N	+	+	+	+	N	N	+	N	+	N	N
ADENOCARCINOMA, NOS	X											X						X							
FIBROADENOMA												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
CARCINOMA,NOS																									
ADENOMA, NOS														X											
UTERUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
PAPILLARY ADENOCARCINOMA																									
ENDOMETRIAL STROMAL POLYP				X				X											X					X	
ENDOMETRIAL STROMAL SARCOMA																								X	
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA											X														
BODY CAVITIES																									
PERITONEUM	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	N	N	N	N	N	N	N	N	N	N	N
MYELOMONOCYTIC LEUKEMIA															X		X		X						

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	106	106	106	106	043	106	103	106	106	106	106	106	106	106	106	106	106	106	106	106	083	106	106	106	106	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BASAL-CELL CARCINOMA					X																					1
SARCOMA, NOS															X											1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA																										1
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BASAL-CELL CARCINOMA, INVASIVE					X																					1
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
SARCOMA, NOS, METASTATIC															X											1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYMUS	+	+	+	+	+	+	-	-	+	-	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	38
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE										X									X						X	4
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	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS	X		X			X	X		X		X	X	X	X	X		X		X	X	X	X	X		X	31
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA														X												1
PHEOCHROMOCYTOMA																										1
THYROID	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-CELL CARCINOMA																					X					1
PARATHYROID	+	+	-	-	+	-	-	-	-	+	-	-	+	-	+	+	+	~	-	-	+	-	-	-	-	22
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	N	+	N	N	+	N	N	+	N	N	+	N	N	N	N	N	+	+	N	+	+	N	N	50
ADENOCARCINOMA, NOS					X																					4
FIBROADENOMA	X			X						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
CARCINOMA,NOS		X																								1
ADENOMA, NOS				X																						2
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PAPILLARY ADENOCARCINOMA	X																									1
ENDOMETRIAL STROMAL POLYP													X					X			X	X	X	X		11
ENDOMETRIAL STROMAL SARCOMA				X			X																			3
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA																										1
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SARCOMA, NOS																										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
MYELOMONOCYTIC LEUKEMIA																										3

* 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 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	100	105	105	081	083	098	086	105	105	105	103	105	104	105	105	105	105	100	105	089	105	105	105	105	105
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS, METASTATIC					X																				
C-CELL CARCINOMA, METASTATIC																			X						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL CARCINOMA, INVASIV																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	-	-	+	-	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																			X						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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA				X													X								
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																	X								
ADENOMA, NOS	X					X	X									X			X	X	X	X		X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA				X																				X	
THYROID	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA											X														
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA																							X		
C-CELL CARCINOMA																			X		X				
PARATHYROID	-	-	-	-	-	-	+	-	-	-	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	N	+	+	N	N	N	+	N	+	N	N	N	+	N	N	+	+	+	N	+	N	+	+
ADENOCARCINOMA, NOS					X														X						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
ADENOMA, NOS			X						X											X					
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
SARCOMA, NOS													X												
ENDOMETRIAL STROMAL POLYP			X		X				X	X		X			X	X	X						X		X
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL TUMOR										X															
GRANULOSA-CELL CARCINOMA																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA							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
MYELOMONOCYTIC LEUKEMIA	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) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	089	105	105	105	105	105	105	105	105	105	088	105	105	100	105	091	103	103	103	103	102	105	105	105	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS, METASTATIC							X																			2
C-CELL CARCINOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULOSA-CELL CARCINOMA, INVASIV																			X							1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	-	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE							X					X			X						X		X		X	8
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRANSITIONAL-CELL PAPILLOMA																										2
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA,NOS																							X			2
ADENOMA, NOS		X	X	X	X	X	X			X	X	X		X	X			X			X	X		X		25
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA																										2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
FOLLICULAR-CELL ADENOMA							X																			2
FOLLICULAR-CELL CARCINOMA												X	X													2
C-CELL ADENOMA	X			X																						3
C-CELL CARCINOMA																										2
PARATHYROID	-	-	-	+	+	-	-	-	-	-	-	+	-	-	-	+	+	+	+	-	-	-	-	-	-	11
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ISLET-CELL ADENOMA																X										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	N	+	+	N	N	N	N	+	+	N	+	N	+	+	+	+	+	N	N	N	N	+	+	N	50M
ADENOCARCINOMA, NOS	X																									4
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	N	N	50M
ADENOMA, NOS																			X							4
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS							X																			1
SARCOMA, NOS																										1
ENDOMETRIAL STROMAL POLYP								X		X				X			X		X							15
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULOSA-CELL TUMOR							X	X																		3
GRANULOSA-CELL CARCINOMA																			X							1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA																				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	N	50M
MYELOMONOCYTIC LEUKEMIA									X	X									X					X		7

* 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 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	105	081	094	105	105	105	105	100	105	105	081	105	105	105	105	105	105	109	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROSARCOMA		X																							
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
FIBROSARCOMA, METASTATIC		X																							
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	-	+	+	+	+	-	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+
THYMOMA																									
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE	X						X	X		X														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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA																									
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS	X		X	X	X	X	X			X		X	X	X	X		X	X			X	X	X		X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA												X					X								
PHEOCHROMOCYTOMA																								X	
GANGLIONEUROMA								X																	
THYROID	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA	X									X		X					X		X						X
FOLLICULAR-CELL CARCINOMA							X																		
C-CELL ADENOMA					X																X				
C-CELL CARCINOMA																						X			
PARATHYROID	+	-	-	-	+	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	+	N	+	N	N	N	N	+	+	+	N	N	N	N	+
ADENOMA, NOS																									
FIBROADENOMA											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
ADENOMA, NOS								X											X						
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
ENDOMETRIAL STROMAL POLYP	X				X	X			X								X				X		X		
ENDOMETRIAL STROMAL SARCOMA			X																						
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL TUMOR								X																	
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA																									
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
MYELOMONOCYTIC LEUKEMIA																		X							

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	104	105	105	105	062	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	50M
SQUAMOUS CELL PAPILLOMA		X									X															2
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	50M
SARCOMA, NOS										X										X						2
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA																	X									1
FIBROSARCOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	+	+	+	-	-	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	47
THYMOMA																								X		1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																X		X						X		3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRANSITIONAL-CELL PAPILLOMA										X																1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA,NOS														X							X					3
ADENOMA, NOS	X	X			X	X	X	X	X	X	X	X	X		X		X	X	X				X		X	34
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																										2
PHEOCHROMOCYTOMA																										1
GANGLIONEUROMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
FOLLICULAR-CELL ADENOMA				X			X		X			X	X	X	X					X		X	X	X		17
FOLLICULAR-CELL CARCINOMA																		X								2
C-CELL ADENOMA		X			X			X														X				6
C-CELL CARCINOMA																										1
PARATHYROID	+	+	-	-	+	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	12
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	+	+	+	N	N	+	+	+	N	+	+	N	+	N	N	+	+	+	N	N	N	50M
ADENOMA, NOS										X																1
FIBROADENOMA					X	X				X				X								X				9
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
ADENOMA, NOS		X				X											X									5
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS										X																1
ENDOMETRIAL STROMAL POLYP						X		X		X						X									X	12
ENDOMETRIAL STROMAL SARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULOSA-CELL TUMOR											X															2
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA																			X	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	N	50M
MYELOMONOCYTIC LEUKEMIA													X													2

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
KERATOACANTHOMA			1 (2%)
*SUBCUT TISSUE	(49)	(50)	(50)
SARCOMA, NOS	4 (8%)	1 (2%)	2 (4%)
NEUROFIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(49)
CARCINOMA, NOS, UNC PRIM OR META		1 (2%)	
HEPATOCELLULAR CARCINOMA, METAST	4 (8%)	1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	12 (24%)	9 (18%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	4 (8%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	7 (14%)	4 (8%)	7 (14%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	1 (2%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
*HEMATOPOIETIC SYSTEM	(49)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#SPLEEN	(49)	(47)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
#LYMPH NODE	(46)	(46)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)	2 (4%)	1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#KIDNEY	(49)	(50)	(50)
MAST-CELL TUMOR	1 (2%)		
CIRCULATORY SYSTEM			
#SPLEEN	(49)	(47)	(50)
HEMANGIOMA	1 (2%)		1 (2%)
HEMANGIOSARCOMA			1 (2%)
ANGIOSARCOMA	5 (10%)	1 (2%)	2 (4%)
#LYMPH NODE	(46)	(46)	(49)
HEMANGIOMA	1 (2%)	4 (9%)	1 (2%)
#HEART	(49)	(49)	(49)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(49)	(50)	(50)
HEMANGIOMA	1 (2%)	2 (4%)	2 (4%)
ANGIOSARCOMA	1 (2%)	3 (6%)	5 (10%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
HEPATOCELLULAR ADENOMA	7 (14%)	10 (20%)	8 (16%)
HEPATOCELLULAR CARCINOMA	10 (20%)	33 (66%)	29 (58%)
SARCOMA, NOS, METASTATIC	1 (2%)		
#PANCREAS	(48)	(49)	(45)
SARCOMA, NOS, INVASIVE	1 (2%)		
#DUODENUM	(45)	(46)	(46)
ADENOMATOUS POLYP, NOS			1 (2%)
#JEJUNUM	(45)	(46)	(46)
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
TUBULAR-CELL ADENOMA		1 (2%)	1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SARCOMA, NOS, INVASIVE	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(43)	(39)
ADENOMA, NOS	2 (5%)	2 (5%)	
#ADRENAL	(48)	(49)	(49)
ADENOMA, NOS	3 (6%)	1 (2%)	
CORTICAL ADENOMA	1 (2%)		
PHEOCHROMOCYTOMA	2 (4%)	12 (24%)	14 (29%)
#THYROID	(47)	(49)	(49)
FOLLICULAR-CELL ADENOMA		3 (6%)	16 (33%)
REPRODUCTIVE SYSTEM			
*SEMINAL VESICLE	(49)	(50)	(50)
SARCOMA, NOS, METASTATIC	1 (2%)		
#TESTIS	(47)	(49)	(50)
INTERSTITIAL-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(49)	(50)	(50)
ADENOMA, NOS		1 (2%)	1 (2%)
CYSTADENOMA, NOS	1 (2%)		
*EAR	(49)	(50)	(50)
SARCOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(50)	(50)
SARCOMA, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
HEAD			
ADENOCARCINOMA, NOS		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	10	19
MORIBUND SACRIFICE	2	2	4
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	39	38	27
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING	1		
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	37	47	45
TOTAL PRIMARY TUMORS	66	100	102
TOTAL ANIMALS WITH BENIGN TUMORS	23	32	31
TOTAL BENIGN TUMORS	31	45	50
TOTAL ANIMALS WITH MALIGNANT TUMORS	25	38	40
TOTAL MALIGNANT TUMORS	34	54	52
TOTAL ANIMALS WITH SECONDARY TUMORS#	5	2	2
TOTAL SECONDARY TUMORS	8	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		1	
TOTAL UNCERTAIN TUMORS		1	

* 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 ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

	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)
SARCOMA, NOS	2 (4%)	3 (6%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	2 (4%)	6 (12%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	2 (4%)
SARCOMA, NOS, METASTATIC	1 (2%)		
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	11 (22%)	23 (46%)	21 (42%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
*HEMATOPOIETIC SYSTEM	(50)	(50)	(50)
NEOPLASM, NOS		2 (4%)	
#SPLEEN	(46)	(48)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)	2 (4%)	3 (6%)
#LYMPH NODE	(46)	(47)	(49)
NEOPLASM, NOS	1 (2%)		
SARCOMA, NOS, INVASIVE			1 (2%)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	3 (6%)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#THYMUS	(26)	(19)	(27)
MALIGNANT LYMPHOMA, NOS			1 (4%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
ANGIOSARCOMA			1 (2%)
#SPLEEN	(46)	(48)	(49)
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
ANGIOSARCOMA	1 (2%)	1 (2%)	2 (4%)
#LYMPH NODE	(46)	(47)	(49)
HEMANGIOMA	1 (2%)		
#HEART	(50)	(50)	(49)
ANGIOSARCOMA	1 (2%)		
#LIVER	(50)	(50)	(50)
HEMANGIOMA	1 (2%)		1 (2%)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
ANGIOSARCOMA			2 (4%)
#UTERUS	(48)	(49)	(49)
HEMANGIOMA			2 (4%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	3 (6%)	9 (18%)	12 (24%)
HEPATOCELLULAR CARCINOMA	1 (2%)	6 (12%)	11 (22%)
#STOMACH	(50)	(49)	(48)
PAPILLOMATOSIS	3 (6%)	1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (2%)	1 (2%)	
URINARY SYSTEM			
#URINARY BLADDER	(49)	(48)	(47)
SARCOMA, NOS			1 (2%)
SARCOMA, NOS, INVASIVE			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(42)	(40)	(39)
ADENOMA, NOS	12 (29%)	8 (20%)	14 (36%)
#ADRENAL	(50)	(49)	(47)
ADENOMA, NOS	2 (4%)	1 (2%)	1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	1 (2%)	
#THYROID	(50)	(47)	(50)
FOLLICULAR-CELL ADENOMA		1 (2%)	13 (26%)
FOLLICULAR-CELL CARCINOMA			2 (4%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
#UTERUS	(48)	(49)	(49)
ADENOMA, NOS	1 (2%)		
SARCOMA, NOS	1 (2%)	1 (2%)	
LEIOMYOSARCOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP			2 (4%)
CARCINOSARCOMA			1 (2%)
#OVARY	(43)	(38)	(34)
PAPILLARY CYSTADENOMA, NOS	1 (2%)		1 (3%)
TUBULAR ADENOMA	2 (5%)	3 (8%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)	1 (2%)	
CYSTADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
SARCOMA, 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
ALL OTHER SYSTEMS			
MULTIPLE SITES			
NEOPLASM, NOS		1	
*MULTIPLE ORGANS	(50)	(50)	(50)
MESOTHELIOMA, INVASIVE			1 (2%)
PLEURAL CAVITY			
MESOTHELIOMA, MALIGNANT			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	11	12	12
MORIBUND SACRIFICE	1	1	2
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	38	37	36
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	47	47
TOTAL PRIMARY TUMORS	51	76	107
TOTAL ANIMALS WITH BENIGN TUMORS	23	23	32
TOTAL BENIGN TUMORS	29	29	52
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	35	39
TOTAL MALIGNANT TUMORS	21	44	55
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	1
TOTAL SECONDARY TUMORS	1	2	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	3	
TOTAL UNCERTAIN TUMORS	1	3	
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 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	093	105	105	105	105	105	105	105	105	105	105	105	105	105	105	091	105	093	102	092	105	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS		X	X																	X	X				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA								X																	X
ALVEOLAR/BRONCHIOLAR ADENOMA		X							X	X	X			X			X						X	
ALVEOLAR/BRONCHIOLAR CARCINOMA																			X						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																									
ANGIOSARCOMA																								X	X
MALIGNANT LYMPHOMA, NOS																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
HEMANGIOMA																								X	
MALIGNANT LYMPHOMA, NOS																	X								
THYMUS	+	+	–	+	–	–	+	–	–	–	+	+	–	–	–	+	–	–	–	–	–	–	+	+	–
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA												X	X										X		
HEPATOCELLULAR CARCINOMA								X		X												X			X
SARCOMA, NOS, METASTATIC																					X				
HEMANGIOMA																									
ANGIOSARCOMA																								X	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	N	N	N	+	+	N	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS, INVASIVE																						X			
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																			X						
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS, INVASIVE																						X			
MAST-CELL TUMOR																									
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	–	+	–	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS														X		X									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS											X		X												
CORTICAL ADENOMA								X																	
PHEOCHROMOCYTOMA													X												
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
PARATHYROID	+	–	+	–	–	–	+	+	+	+	+	+	–	+	+	+	+	–	–	+	–	–	+	–	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SEMINAL VESICLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS, METASTATIC																						X			
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CYSTADENOMA, NOS																									
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS								X																	
BODY CAVITIES																									
PERITONEUM	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	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS		X			X																				
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	064	105	105	090	105	105	105	105	105	105	105	105	105	105	105	105	094	105	105	099	105	105	105	097	105	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49M
SARCOMA, NOS																										4
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA																			X		X					4
ALVEOLAR/BRONCHIOLAR ADENOMA						X					X	X									X			X		12
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
HEMANGIOMA																						X				1
ANGIOSARCOMA								X												X				X		5
MALIGNANT LYMPHOMA, NOS													X													1
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	M	+	+	+	+	-	+	+	+	46
HEMANGIOMA																										1
MALIGNANT LYMPHOMA, NOS																										1
THYMUS	-	-	+	-	-	-	+	+	+	+	+	-	-	+	+	-	M	-	-	-	-	-	+	-	-	18
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA													X		X							X	X			7
HEPATOCELLULAR CARCINOMA		X		X				X			X								X		X					10
SARCOMA, NOS, METASTATIC																										1
HEMANGIOMA			X																							1
ANGIOSARCOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	N	N	+	N	+	+	+	+	N	N	+	+	+	+	M	+	N	N	N	N	+	+	N	49M
PANCREAS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
SARCOMA, NOS, INVASIVE																										1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	-	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	-	+	+	+	-	+	45
ADENOCARCINOMA, NOS																										1
LARGE INTESTINE	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	-	+	+	+	-	+	43
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
SARCOMA, NOS, INVASIVE																										1
MAST-CELL TUMOR														X												1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	-	+	+	+	+	+	+	+	+	-	+	-	+	-	+	+	M	+	+	+	+	+	+	+	+	41
ADENOMA, NOS																										2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	M	+	+	+	+	+	+	+	+	48
ADENOMA, NOS														X												3
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA			X																							2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	-	47
PARATHYROID	-	+	-	+	-	+	-	-	+	+	-	-	-	+	+	-	M	+	-	-	-	+	-	-	-	24
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	49M
TESTIS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
PROSTATE	-	-	-	+	-	+	+	+	+	+	+	+	-	-	+	+	M	+	+	+	-	+	+	+	-	40
SEMINAL VESICLE	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	N	+	+	+	+	49M
SARCOMA, NOS, METASTATIC																										1
NERVOUS SYSTEM																										
BRAIN	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	49M
CYSTADENOMA, NOS													X													1
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	49M
SARCOMA, NOS																										1
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	49M
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	M	N	N	N	N	N	N	N	N	49M
MALIGNANT LYMPHOMA, NOS	X		X	X																	X					7
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																		X								1

M ANIMALS NECROPSIED

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

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

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	076	105	105	051	105	105	105	089	105	105	105	105	105	105	105	090	105	105	105	091	086	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
NEUROFIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, UNC PRIM OR META									X																
HEPATOCELLULAR CARCINOMA, METASTA																						X			
ALVEOLAR/BRONCHIOLAR ADENOMA		X	X							X					X								X		
ALVEOLAR/BRONCHIOLAR CARCINOMA						X																			X
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
ANGIOSARCOMA						X																			
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+
HEMANGIOMA																	X								
MALIGNANT LYMPHOMA, NOS														X											
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
THYMUS	-	-	-	+	-	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-	
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA										X	X	X								X	X	X			
HEPATOCELLULAR CARCINOMA	X		X	X	X	X	X		X					X		X	X	X	X				X	X	X
HEMANGIOMA																									
ANGIOSARCOMA						X																			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	N	N	+	+	N	+	N	+	N	+	N	+	+	N	+	+	+	+	+	N	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
ADENOCARCINOMA, NOS																									X
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA																							X		
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS									X																
PHEOCHROMOCYTOMA							X							X								X		X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA										X									X						
PARATHYROID	+	+	-	-	+	+	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	+	+	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																	X								
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
ADENOCARCINOMA, NOS, METASTATIC																									
MALIGNANT LYMPHOMA, NOS	X															X									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																									
HEAD NOS																									
ADENOCARCINOMA, NOS																									

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

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

ANIMAL NUMBER	02607	02708	02909	03001	03102	03305	03405	03505	03605	03705	03805	03905	04001	04102	04205	04405	04505	04605	04705	04805	04905	05005	TOTAL
WEEKS ON STUDY	10 3	10 5	10 4	10 5	09 8	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	09 5	08 3	06 7	07 8	09 6	10 5	10 5	10 5	TISSUES TUMORS
INTEGUMENTARY SYSTEM																							
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	50M
SARCOMA, NOS																							1
NEUROFIBROSARCOMA																		X					1
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA, NOS, UNC PRIM OR META																							1
HEPATOCELLULAR CARCINOMA, METASTA																							1
ALVEOLAR/BRONCHIOLAR ADENOMA										X	X				X						X		3
ALVEOLAR/BRONCHIOLAR CARCINOMA			X																		X		1
TRACHEA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																							
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ANGIOSARCOMA																							1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	~	+	+	-	+	+	+	46
HEMANGIOMA										X	X												4
MALIGNANT LYMPHOMA, NOS																	X				X		2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE												X											1
THYMUS	-	-	-	-	-	-	-	-	+	+	+	-	-	+	+	-	+	-	-	-	-	+	11
CIRCULATORY SYSTEM																							
HEART	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA				X	X			X													X		10
HEPATOCELLULAR CARCINOMA	X	X	X			X				X	X	X	X	X	X	X	X			X	X	X	33
HEMANGIOMA		X											X										2
ANGIOSARCOMA					X										X								3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	N	N	+	+	+	50M
PANCREAS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	46
ADENOCARCINOMA, NOS																							1
LARGE INTESTINE	-	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	-	-	+	+	+	-	44
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA																							1
URINARY BLADDER	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																							
PITUITARY	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	43
ADENOMA, NOS																					X	X	2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
ADENOMA, NOS																							1
PHEOCHROMOCYTOMA	X								X	X		X			X					X	X	X	12
THYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																X							3
PARATHYROID	-	+	-	+	-	+	-	-	-	+	-	+	+	-	-	-	+	-	+	-	+	-	19
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	50M
TESTIS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PROSTATE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																							
BRAIN	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	50M
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	50M
ADENOCARCINOMA, NOS, METASTATIC																		X					1
MALIGNANT LYMPHOMA, NOS		X									X												4
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																					X		1
MALIGNANT LYMPHOMA, MIXED TYPE																						X	1
HEAD NOS																							
ADENOCARCINOMA, NOS																		X					1

M ANIMALS NECROPSIED

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

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

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

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	094	094	074	104	104	104	104	104	104	087	053	104	104	104	021	104	104	094	104	104	104	097	096
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																									
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA															X									X	
HEMANGIOSARCOMA																									
ANGIOSARCOMA		X																							
MALIG LYMPHOMA, LYMPHOCYTIC TYPE																							X		
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
HEMANGIOMA																									
MALIGNANT LYMPHOMA, NOS													X												
THYMUS	-	-	-	-	+	-	-	-	-	+	-	-	-	+	+	-	-	+	-	-	-	-	-	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																								X	
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA						X			X								X	X						X	
HEPATOCELLULAR CARCINOMA	X	X	X				X	X		X	X			X	X	X			X	X	X	X	X		
HEMANGIOMA		X																	X						
ANGIOSARCOMA						X									X			X						X	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	N	N	N	N	N	+	+	+	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+
ADENOMATOUS POLYP, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	-	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA																									
URINARY BLADDER	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	-	-	+	-	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
PHEOCHROMOCYTOMA			X			X			X		X				X	X			X				X		
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA		X	X				X		X		X					X						X		X	
PARATHYROID	-	-	-	+	-	-	-	+	+	-	-	-	-	-	+	-	+	-	-	-	+	+	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR																									
PROSTATE	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS					X							X						X		X					X
MALIG LYMPHOMA, HISTIOCYTIC TYPE																									
HEMATOPOIETIC SYSTEM																									
MALIGNANT LYMPHOMA, NOS																	X								

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

TABLE 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
WEEKS ON STUDY	104	104	104	088	104	102	104	039	093	104	104	104	104	076	104	071	095	104	069	081	104	104	104	097	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	50
KERATOACANTHOMA																									X	1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	50
SARCOMA, NOS						X																		X		2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	~	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA									X								X									2
ALVEOLAR/BRONCHIOLAR ADENOMA					X		X														X					3
ALVEOLAR/BRONCHIOLAR CARCINOMA										X																1
TRACHEA	+	+	+	+	+	~	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	~	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	46
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOMA																										1
HEMANGIOSARCOMA																										1
ANGIOSARCOMA													X													2
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOMA													X													1
MALIGNANT LYMPHOMA, NOS																										1
THYMUS	-	-	+	~	-	~	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	+	9
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	~	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA																										1
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	~	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA		X																		X		X				8
HEPATOCELLULAR CARCINOMA			X		X	X	X		X	X	X	X	X	X			X	X			X		X			29
HEMANGIOMA																										2
ANGIOSARCOMA														X												5
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	N	+	+	+	+	N	+	+	N	+	+	N	+	+	N	+	N	+	N	+	50
PANCREAS	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	45
ESOPHAGUS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ADENOMATOUS POLYP, NOS			X																							1
LARGE INTESTINE	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA										X																1
URINARY BLADDER	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	-	+	+	-	-	+	+	+	-	+	39
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA					X	X				X			X				X	X								14
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA	X					X	X		X			X						X					X	X		16
PARATHYROID	-	-	-	-	-	-	+	-	-	+	-	+	-	+	-	-	+	-	+	-	-	-	+	-	-	16
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR						X																				1
PROSTATE	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	~	+	+		44
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
ADENOMA, NOS										X																1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
MALIGNANT LYMPHOMA, NOS																			X		X					7
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																X										1
HEMATOPOIETIC SYSTEM																										
MALIGNANT LYMPHOMA, NOS																										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 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	105	105	071	105	105	105	105	105	105	104	080	088	105	105	105	105	084	091	105	105	091
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS														X											
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																								X	
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
SARCOMA, NOS, METASTATIC														X											
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+
ANGIOSARCOMA																					X				
MALIGNANT LYMPHOMA, NOS																									
LYMPH NODES	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
NEOPLASM, NOS																						X			
HEMANGIOMA																									
MALIGNANT LYMPHOMA, NOS								X																	
THYMUS	-	-	-	+	+	+	-	-	-	-	+	+	+	-	-	-	+	+	-	+	+	-	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ANGIOSARCOMA																					X				
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA	X	X																							
HEPATOCELLULAR CARCINOMA																									
HEMANGIOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	+	+	+	+	+	N	N	N	+	+	+	+	+	N	+	+	+
PANCREAS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMATOSIS											X														
SQUAMOUS CELL CARCINOMA																			X						
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	-
ADENOMA, NOS		X	X					X				X		X			X	X	X						
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									X
PHEOCHROMOCYTOMA											X														
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
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ADENOMA, NOS								X																	
SARCOMA, NOS																									
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+
PAPILLARY CYSTADENOMA, NOS																									
TUBULAR ADENOMA						X																			
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS	X																								
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS							X				X		X	X										X	

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

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

ANIMAL NUMBER	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	0 8 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 9 9	1 0 5	1 0 5	1 0 5	0 5 4	1 0 5	0 8 3	1 0 5	1 0 5	1 0 5	1 0 5	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS																						X				2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+,	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
SARCOMA, NOS, METASTATIC														X												1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	46
ANGIOSARCOMA																										1
MALIGNANT LYMPHOMA, NOS																						X				1
LYMPH NODES	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	46
NEOPLASM, NOS																										1
HEMANGIOMA								X																		1
MALIGNANT LYMPHOMA, NOS																										1
THYMUS	+	+	-	-	-	-	+	-	-	+	-	-	+	+	-	-	+	+	+	+	-	+	+	+	+	26
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ANGIOSARCOMA																										1
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																				X						3
HEPATOCELLULAR CARCINOMA																					X					1
HEMANGIOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	N	+	+	N	+	N	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	X	+	+	+	50
PAPILLOMATOSIS																										3
SQUAMOUS CELL CARCINOMA																										1
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	+	+	+	+	+	45
LARGE INTESTINE	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	45
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	-	-	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	42
ADENOMA, NOS							X						X											X	X	12
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS																				X						2
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	50M
UTERUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOMA, NOS																										1
SARCOMA, NOS																					X					1
OVARY	+	-	-	-	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	43
PAPILLARY CYSTADENOMA, NOS																				X						1
TUBULAR ADENOMA																		X								2
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
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	50M
MALIGNANT LYMPHOMA, NOS							X					X		X	X								X	X		11

M ANIMALS NECROPSIED

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

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

LOW DOSE

ANIMAL NUMBER	00112	00213	00314	00415	00516	00617	00718	00819	00920	01121	01222	01323	01424	01525	01626	01727	01828	01929	02030	02232	02333	02434	02535
WEEKS ON STUDY	09205	10105	10105	10105	10105	10105	10105	10105	10900	10105	10205	10105	10105	10105	10737	10905	10203	10105	10105	10805	11005	10105	10904
INTEGUMENTARY SYSTEM																							
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS															X							X	
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																							
ALVEOLAR/BRONCHIOLAR ADENOMA										X													
ALVEOLAR/BRONCHIOLAR CARCINOMA																							
OSTEOSARCOMA, METASTATIC																							
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
HEMANGIOMA					X																		
HEMANGIOSARCOMA																							
ANGIOSARCOMA																		X					
MALIGNANT LYMPHOMA, NOS																							
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–
MALIGNANT LYMPHOMA, NOS									X														
MALIG.LYMPHOMA, HISTIOCYTIC TYPE														X									
THYMUS	–	–	–	+	+	+	–	+	–	+	–	+	–	–	–	–	–	–	+	+	+	–	–
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA					X						X		X					X					
HEPATOCELLULAR CARCINOMA														X	X				X				
HEMANGIOSARCOMA																					X		
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+	+	N	+	+	+	+	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	–
ESOPHAGUS	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMATOSIS							X																
SQUAMOUS CELL CARCINOMA													X										
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
ENDOCRINE SYSTEM																							
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	+	+	–	+	–
ADENOMA, NOS		X	X			X				X													+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																							
PHEOCHROMOCYTOMA																							
THYROID	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA					X																		
PARATHYROID	+	–	+	–	–	–	–	–	–	–	+	+	–	+	+	+	–	–	+	+	+	–	+
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND	N	+	+	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N	+
ADENOCARCINOMA, NOS																							N
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
SARCOMA, NOS																							
OVARY	–	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	–	+	–	–
TUBULAR ADENOMA																			X				–
NERVOUS SYSTEM																							
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																							
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS				X																			
CYSTADENOMA, NOS																							
ALL OTHER SYSTEMS																							
MULTIPLE SITES NOS																							
NEOPLASM, NOS																							
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS	X		X			X	X	X							X					X	X		
MALIGNANT LYMPHOMA, MIXED TYPE																			X				
HEMATOPOIETIC SYSTEM																							
NEOPLASM, NOS											X												X

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

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY LOW DOSE

ANIMAL NUMBER / WEEKS ON STUDY	026 100	027 105	028 105	029 105	030 105	031 096	032 105	033 085	034 085	035 105	036 105	037 105	038 099	039 105	040 105	041 105	042 105	043 105	044 105	045 105	046 105	047 105	048 086	049 095	050 069	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS								X																		3
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA													X													1
ALVEOLAR/BRONCHIOLAR ADENOMA										X																2
ALVEOLAR/BRONCHIOLAR CARCINOMA					X																					1
OSTEOSARCOMA, METASTATIC			X																							1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
HEMANGIOMA																										1
HEMANGIOSARCOMA						X																				1
ANGIOSARCOMA																										1
MALIGNANT LYMPHOMA, NOS							X												X							2
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47
MALIGNANT LYMPHOMA, NOS																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
THYMUS	+	-	-	-	-	-	-	-	-	-	+	+	-	+	-	-	+	-	-	~	+	+	-	+	-	19
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA													X				X		X							9
HEPATOCELLULAR CARCINOMA			X								X		X							X						6
HEMANGIOSARCOMA						X																				1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	N	+	N	N	N	+	+	N	+	+	+	+	+	+	+	+	+	N	+	N	50M
PANCREAS	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	44
ESOPHAGUS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PAPILLOMATOSIS																										1
SQUAMOUS CELL CARCINOMA																										1
SMALL INTESTINE	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	-	+	+	-	+	+	+	+	~	+	+	+	+	-	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	+	+	+	-	40
ADENOMA, NOS										X				X		X						X				8
ADRENAL	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS									•													X				1
PHEOCHROMOCYTOMA								X																		1
THYROID	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
FOLLICULAR-CELL ADENOMA																										1
PARATHYROID	+	-	-	-	+	-	-	~	-	+	+	+	-	+	+	-	+	+	-	-	-	-	+	-	-	23
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
ADENOCARCINOMA, NOS	X																									1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SARCOMA, NOS			X																							1
OVARY	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	-	+	-	+	+	+	-	+	+	38
TUBULAR ADENOMA							X					X														3
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
ADENOMA, NOS																										1
CYSTADENOMA, NOS					X																					1
ALL OTHER SYSTEMS																										
MULTIPLE SITES NOS																									X	1
NEOPLASM, NOS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MALIGNANT LYMPHOMA, NOS	X			X					X	X	X	X	X	X	X		X	X			X	X	X	X		23
MALIGNANT LYMPHOMA, MIXED TYPE																										1
HEMATOPOIETIC SYSTEM																										
NEOPLASM, NOS																										2

M ANIMALS NECROPSIED

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

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

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	0961	1041	0721	1041	1041	0901	1041	1041	1041	1041	0941	1041	1041	1041	0831	1041	0701	1041	1041	1041	1051	0861	0911	1041	1041
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ANGIOSARCOMA					X																				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA				X									X												X
ALVEOLAR/BRONCHIOLAR CARCINOMA																							X		
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ANGIOSARCOMA					X								X												
MALIGNANT LYMPHOMA, NOS				X																	X				
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
SARCOMA, NOS, INVASIVE																									
MALIGNANT LYMPHOMA, NOS	X																							X	
MALIG.LYMPHOMA, UNDIFFER-TYPE																									
THYMUS	+	-	+	-	-	-	-	+	+	+	+	-	+	+	+	+	-	-	+	+	-	-	-	+	+
MALIGNANT LYMPHOMA, NOS																									X
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA		X			X			X	X					X		X		X	X						
HEPATOCELLULAR CARCINOMA				X			X					X											X		
HEMANGIOMA												X													
HEMANGIOSARCOMA					X																				
ANGIOSARCOMA										X															
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	N	N	+	+	+	N	+	+	+	+	+	N	+	+	+	+	N	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+
LARGE INTESTINE	+	+	-	+	+	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
SARCOMA, NOS															X										
SARCOMA, NOS, INVASIVE																									
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-	-	+	-	+	+	-	-
ADENOMA, NOS				X	X	X		X			X	X				X									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ADENOMA, NOS							X																		
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA			X	X	X		X		X		X					X				X					
FOLLICULAR-CELL CARCINOMA												X													
PARATHYROID	+	-	-	-	-	-	-	-	-	-	-	+	+	+	-	-	-	-	-	+	-	-	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	+	N	N	+	N	+	N	N	N	+
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
LEIOMYOSARCOMA										X															
ENDOMETRIAL STROMAL POLYP												X													
CARCINOSARCOMA																					X				
HEMANGIOMA					X		X																		
OVARY	+	+	+	-	+	+	+	-	+	+	-	-	+	+	+	+	-	+	+	+	+	-	-	+	+
PAPILLARY CYSTADENOMA, NOS	X																								
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
MESOTHELIOMA, MALIGNANT																									
PERITONEUM	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																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, INVASIVE																									
MALIGNANT LYMPHOMA, NOS		X				X				X	X		X			X			X		X	X			

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

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

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	105	058	105	064	105	104	105	092	105	105	105	100	105	105	105	105	105	105	105	105	105	105	105	105	083	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
ANGIOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA					X															X				X		6
ALVEOLAR/BRONCHIOLAR CARCINOMA																							X			2
TRACHEA	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	-	+	-	+		44
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ANGIOSARCOMA																										2
MALIGNANT LYMPHOMA, NOS																			X							3
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SARCOMA, NOS, INVASIVE																					X					1
MALIGNANT LYMPHOMA, NOS																									X	3
MALIG LYMPHOMA, UNDIFFER-TYPE							X																			1
THYMUS	+	-	-	-	+	-	+	-	-	+	+	-	+	+	+	-	+	+	-		-	+	+	+	-	27
MALIGNANT LYMPHOMA, NOS																										1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA								X						X							X			X		12
HEPATOCELLULAR CARCINOMA	X		X						X		X				X	X							X			11
HEMANGIOMA																										1
HEMANGIOSARCOMA																										1
ANGIOSARCOMA																X										2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	N	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	N	50M
PANCREAS	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ESOPHAGUS	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
STOMACH	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
LARGE INTESTINE	+	-	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+		41
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SARCOMA, NOS																										1
SARCOMA, NOS, INVASIVE																					X					1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	39
ADENOMA, NOS									X	X	X	X		X				X				X				14
ADRENAL	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
ADENOMA, NOS																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA										X	X			X	X										X	13
FOLLICULAR-CELL CARCINOMA									X																	2
PARATHYROID	+	+	-	-	+	-	+	-	-	+	-	-	-	-	-	-	+	-	-	-	+	+	-	+	+	17
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	39M
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LEIOMYOSARCOMA																										1
ENDOMETRIAL STROMAL POLYP																	X									2
CARCINOSARCOMA																										1
HEMANGIOMA																										2
OVARY	-	+	-	-	+	+	-	-	+	+	-	+	+	+	+	-	+	+	+	-	-	+	+	+	+	34
PAPILLARY CYSTADENOMA, NOS																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
BODY CAVITIES																										
PLEURA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MESOTHELIOMA, MALIGNANT																					X					1
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
SARCOMA, NOS																					X					1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MESOTHELIOMA, INVASIVE																					X					1
MALIGNANT LYMPHOMA, NOS	X	X			X	X		X		X	X	X			X					X			X			21

M ANIMALS NECROPSIED

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

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	1 (2%)
INFLAMMATION, NOS			2 (4%)
INFLAMMATION, NECROTIZING	1 (2%)		
HYPERPLASIA, EPITHELIAL		4 (8%)	
HYPERPLASIA, BASAL CELL	1 (2%)	2 (4%)	
HYPERKERATOSIS	2 (4%)	4 (8%)	2 (4%)
ACANTHOSIS		1 (2%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
FIBROSIS			1 (2%)
NECROSIS, NOS		1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, FOCAL	2 (4%)		1 (2%)
#LUNG	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
BRONCHOPNEUMONIA, NOS			1 (2%)
INFLAMMATION, NOS	5 (10%)	12 (24%)	6 (12%)
INFLAMMATION, DIFFUSE		1 (2%)	
REACTION, FOREIGN BODY			2 (4%)
FIBROSIS		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(49)	(50)	(49)
FIBROSIS, FOCAL	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
LYMPHOID DEPLETION	3 (6%)	11 (22%)	1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HEMATOPOIESIS	36 (73%)	32 (64%)	40 (82%)
#LYMPH NODE	(49)	(48)	(48)
INFLAMMATION, NOS	1 (2%)		
LYMPHOID DEPLETION	1 (2%)	4 (8%)	
ANGIECTASIS		2 (4%)	
PLASMACYTOSIS		2 (4%)	
HYPERPLASIA, RETICULUM CELL		2 (4%)	
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
MINERALIZATION		1 (2%)	2 (4%)
THROMBOSIS, NOS		1 (2%)	
FIBROSIS	2 (4%)	3 (6%)	2 (4%)
PERIARTERITIS			1 (2%)
PERIVASCULITIS		1 (2%)	
DEGENERATION, NOS		1 (2%)	
#MYOCARDIUM	(50)	(50)	(50)
DEGENERATION, NOS	46 (92%)	42 (84%)	44 (88%)
*ARTERY	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
PERIARTERITIS	2 (4%)		1 (2%)
PERIVASCULITIS		1 (2%)	
DIGESTIVE SYSTEM			
*INTESTINAL TRACT	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
FIBROSIS		1 (2%)	
NECROSIS, DIFFUSE		1 (2%)	
#LIVER	(50)	(50)	(50)
DILATATION, NOS	1 (2%)	6 (12%)	10 (20%)
INFLAMMATION, NOS		1 (2%)	1 (2%)
INFLAMMATION, FOCAL		1 (2%)	
FIBROSIS			1 (2%)
NECROSIS, 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
NECROSIS, FOCAL		1 (2%)	3 (6%)
NECROSIS, ISCHEMIC	1 (2%)		
METAMORPHOSIS FATTY	14 (28%)	28 (56%)	33 (66%)
BASOPHILIC CYTO CHANGE	16 (32%)	2 (4%)	5 (10%)
FOCAL CELLULAR CHANGE	14 (28%)	38 (76%)	36 (72%)
CLEAR-CELL CHANGE	2 (4%)		
#BILE DUCT	(50)	(50)	(50)
INFLAMMATION, NOS	16 (32%)	14 (28%)	26 (52%)
HYPERPLASIA, NOS	35 (70%)	39 (78%)	43 (86%)
#PANCREATIC ACINUS	(49)	(49)	(47)
ATROPHY, NOS	3 (6%)	2 (4%)	2 (4%)
ATROPHY, FOCAL	4 (8%)	5 (10%)	3 (6%)
HYPERTROPHY, FOCAL			1 (2%)
HYPERPLASIA, FOCAL		2 (4%)	
#STOMACH	(49)	(50)	(49)
MINERALIZATION		1 (2%)	
INFLAMMATION, NOS	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
FIBROSIS		1 (2%)	
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL	2 (4%)	2 (4%)	1 (2%)
HYPERPLASIA, EPITHELIAL	2 (4%)	8 (16%)	3 (6%)
HYPERKERATOSIS	4 (8%)	3 (6%)	4 (8%)
ACANTHOSIS		2 (4%)	2 (4%)
#GASTRIC SUBMUCOSA	(49)	(50)	(49)
EDEMA, NOS	1 (2%)	1 (2%)	
INFLAMMATION, NOS	1 (2%)		
#PEYER'S PATCH	(49)	(48)	(49)
HYPERPLASIA, NOS	5 (10%)	14 (29%)	10 (20%)
#JEJUNUM	(49)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	
#ILEUM	(49)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	
FIBROSIS		1 (2%)	
#COLON	(47)	(49)	(49)
PARASITISM	1 (2%)	5 (10%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION	9 (18%)	10 (20%)	19 (38%)
INFLAMMATION, NOS		5 (10%)	1 (2%)
INFLAMMATION, INTERSTITIAL			1 (2%)
FIBROSIS, FOCAL			1 (2%)
FIBROSIS, DIFFUSE	3 (6%)	22 (44%)	5 (10%)
NEPHROPATHY	49 (98%)	49 (98%)	48 (96%)
GLOMERULOSCLEROSIS, NOS		3 (6%)	
NECROSIS, MEDULLARY	1 (2%)		
HYPERPLASIA, TUBULAR CELL		1 (2%)	
#RENAL PAPILLA	(50)	(50)	(50)
MINERALIZATION	2 (4%)	3 (6%)	3 (6%)
INFLAMMATION, NOS			2 (4%)
NECROSIS, NOS		1 (2%)	
#KIDNEY/TUBULE	(50)	(50)	(50)
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		1 (2%)
#URINARY BLADDER	(49)	(50)	(48)
HEMORRHAGE	1 (2%)		1 (2%)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, ACUTE	1 (2%)		
NECROSIS, NOS	1 (2%)		
*URETHRAL GLAND	(50)	(50)	(50)
ANGIECTASIS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(47)	(49)
DILATATION, NOS	1 (2%)	1 (2%)	
HEMORRHAGE		1 (2%)	
HYPERPLASIA, NOS	1 (2%)	1 (2%)	1 (2%)
#ADRENAL	(50)	(49)	(49)
DILATATION, NOS		10 (20%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, NOS	1 (2%)		
METAMORPHOSIS FATTY		6 (12%)	
#ADRENAL CORTEX	(50)	(49)	(49)
HYPERTROPHY, NOS	1 (2%)	1 (2%)	
HYPERTROPHY, FOCAL		13 (27%)	2 (4%)
HYPERPLASIA, NOS		2 (4%)	
HYPERPLASIA, FOCAL	2 (4%)		
#ADRENAL MEDULLA	(50)	(49)	(49)
HYPERPLASIA, NOS	6 (12%)	7 (14%)	5 (10%)
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
#THYROID	(49)	(47)	(48)
MINERALIZATION			1 (2%)
CYSTIC FOLLICLES		1 (2%)	
FOLLICULAR CYST, NOS	1 (2%)	2 (4%)	3 (6%)
HYPERPLASIA, C-CELL	4 (8%)	2 (4%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	2 (4%)	3 (6%)
#PARATHYROID	(17)	(16)	(14)
HYPERPLASIA, NOS		1 (6%)	
#PANCREATIC ISLETS	(49)	(49)	(47)
HYPERPLASIA, NOS		2 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	3 (6%)	1 (2%)	
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)		2 (4%)
METAPLASIA, SQUAMOUS	1 (2%)		
#PROSTATE	(47)	(50)	(44)
MINERALIZATION	1 (2%)		
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS	13 (28%)	18 (36%)	9 (20%)
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, ACUTE	1 (2%)		
FIBROSIS, DIFFUSE		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
NECROSIS, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		2 (5%)
HYPERPLASIA, FOCAL	2 (4%)		
#TESTIS	(49)	(50)	(50)
MINERALIZATION	27 (55%)	20 (40%)	25 (50%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS	1 (2%)		
ATROPHY, NOS	19 (39%)	27 (54%)	21 (42%)
HYPERPLASIA, INTERSTITIAL CELL	3 (6%)	6 (12%)	
#TESTIS/TUBULE	(49)	(50)	(50)
ATROPHY, FOCAL	13 (27%)	8 (16%)	14 (28%)
HYPERTROPHY, FOCAL	1 (2%)		
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(49)
MINERALIZATION		1 (2%)	
HYDROCEPHALUS, NOS	1 (2%)	2 (4%)	
HEMORRHAGE		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
OMENTUM			
INFLAMMATION, GRANULOMATOUS		1	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FAT	2	2	

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 ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, NECROTIZING	1 (2%)		
NECROSIS, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
HYPERKERATOSIS			2 (4%)
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
NECROSIS, NOS	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL	1 (2%)		
#LUNG	(50)	(50)	(50)
MINERALIZATION			2 (4%)
HEMORRHAGE		1 (2%)	
BRONCHOPNEUMONIA, NOS	1 (2%)	1 (2%)	
INFLAMMATION, NOS	8 (16%)	10 (20%)	18 (36%)
INFLAMMATION, FOCAL	1 (2%)		
INFLAMMATION, GRANULOMATOUS			1 (2%)
FIBROSIS, DIFFUSE		1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMATOPOIESIS	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
#SPLEEN	(49)	(50)	(50)
LYMPHOID DEPLETION	1 (2%)	7 (14%)	5 (10%)
HEMATOPOIESIS	40 (82%)	38 (76%)	45 (90%)
#LYMPH NODE	(48)	(50)	(49)
LYMPHOID DEPLETION			1 (2%)
ANGIECTASIS			1 (2%)
PLASMACYTOSIS			1 (2%)
HYPERPLASIA, LYMPHOID		4 (8%)	8 (16%)
HEMATOPOIESIS		1 (2%)	
CIRCULATORY SYSTEM			
#LUNG	(50)	(50)	(50)
PERIVASCULITIS		1 (2%)	
#HEART	(50)	(50)	(50)
EMBOLISM, NOS			1 (2%)
FIBROSIS		2 (4%)	2 (4%)
#MYOCARDIUM	(50)	(50)	(50)
DEGENERATION, NOS	40 (80%)	30 (60%)	35 (70%)
#ENDOCARDIUM	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
DILATATION, NOS	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, NOS		2 (4%)	2 (4%)
FIBROSIS			1 (2%)
NECROSIS, FOCAL	1 (2%)	1 (2%)	6 (12%)
NECROSIS, ISCHEMIC	1 (2%)		
METAMORPHOSIS FATTY	7 (14%)	20 (40%)	11 (22%)
BASOPHILIC CYTO CHANGE	41 (82%)	29 (58%)	37 (74%)
FOCAL CELLULAR CHANGE	5 (10%)	17 (34%)	10 (20%)
#BILE DUCT	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)	6 (12%)	15 (30%)
HYPERPLASIA, NOS	12 (24%)	15 (30%)	34 (68%)
#PANCREAS	(47)	(48)	(49)
DEGENERATION, CYSTIC			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
#PANCREATIC ACINUS	(47)	(48)	(49)
ATROPHY, NOS	1 (2%)		1 (2%)
ATROPHY, FOCAL	3 (6%)	3 (6%)	4 (8%)
#ESOPHAGUS	(45)	(47)	(47)
HYPERKERATOSIS		1 (2%)	
#STOMACH	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	1 (2%)
NECROSIS, NOS	1 (2%)	2 (4%)	
HYPERPLASIA, EPITHELIAL	5 (10%)	3 (6%)	3 (6%)
HYPERPLASIA, BASAL CELL	1 (2%)	1 (2%)	
HYPERKERATOSIS	2 (4%)	5 (10%)	3 (6%)
ACANTHOSIS		2 (4%)	3 (6%)
#PEYER'S PATCH	(47)	(48)	(50)
HYPERPLASIA, NOS	2 (4%)	9 (19%)	13 (26%)
#JEJUNUM	(47)	(48)	(50)
INFLAMMATION, ACUTE		1 (2%)	
FIBROSIS		1 (2%)	
#COLON	(47)	(46)	(49)
PARASITISM		3 (7%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION	22 (44%)	20 (40%)	12 (24%)
HYDRONEPHROSIS		1 (2%)	
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)		
NEPHROPATHY	44 (88%)	45 (90%)	44 (88%)
INFARCT, NOS		1 (2%)	
#RENAL PAPILLA	(50)	(50)	(50)
MINERALIZATION	1 (2%)	1 (2%)	11 (22%)
INFLAMMATION, NOS		1 (2%)	
NECROSIS, FOCAL	1 (2%)		
#URINARY BLADDER	(48)	(50)	(50)
HYPERPLASIA, EPITHELIAL		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
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(49)	(49)
DILATATION, NOS		5 (10%)	3 (6%)
HYPERPLASIA, NOS		1 (2%)	2 (4%)
#ADRENAL	(50)	(50)	(50)
DILATATION, NOS		7 (14%)	
HEMORRHAGE			1 (2%)
METAMORPHOSIS FATTY	1 (2%)	8 (16%)	7 (14%)
#ADRENAL CORTEX	(50)	(50)	(50)
HYPERTROPHY, FOCAL	2 (4%)	13 (26%)	3 (6%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)	6 (12%)	1 (2%)
#THYROID	(47)	(47)	(48)
FOLLICULAR CYST, NOS		3 (6%)	7 (15%)
HYPERPLASIA, C-CELL	5 (11%)	3 (6%)	4 (8%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	3 (6%)	8 (17%)
#PARATHYROID	(22)	(11)	(12)
HYPERPLASIA, NOS	1 (5%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	6 (12%)	8 (16%)	7 (14%)
INFLAMMATION, NOS			1 (2%)
FIBROSIS			1 (2%)
NECROSIS, NOS		1 (2%)	
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
*CLITORAL GLAND	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	4 (8%)
#UTERUS	(48)	(50)	(50)
HYDROMETRA		3 (6%)	1 (2%)
INFLAMMATION, NOS	2 (4%)	5 (10%)	1 (2%)
PYOMETRA	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
NECROSIS, NOS	1 (2%)		1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
#UTERUS/ENDOMETRIUM	(48)	(50)	(50)
HYPERPLASIA, NOS	2 (4%)	2 (4%)	1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
#OVARY	(50)	(50)	(50)
CYST, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HYDROCEPHALUS, NOS		2 (4%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
CATARACT		1 (2%)	
*EYE/RETINA	(50)	(50)	(50)
DEGENERATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
OMENTUM			
NECROSIS, FAT	2	2	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 ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
INFLAMMATION, NOS	2 (4%)	1 (2%)	
INFLAMMATION, NECROTIZING			1 (2%)
HYPERKERATOSIS		1 (2%)	
*SUBCUT TISSUE	(49)	(50)	(50)
MINERALIZATION	1 (2%)		1 (2%)
INFLAMMATION, NOS		3 (6%)	1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
FIBROSIS		1 (2%)	
NECROSIS, NOS	1 (2%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(49)	(49)	(49)
INFLAMMATION, NOS	1 (2%)		1 (2%)
INFLAMMATION, FOCAL	1 (2%)		
#LUNG/BRONCHIOLE	(49)	(49)	(49)
INFLAMMATION, FOCAL			1 (2%)
#LUNG	(49)	(49)	(49)
MINERALIZATION		2 (4%)	
HEMORRHAGE	2 (4%)		
INFLAMMATION, NOS	6 (12%)	2 (4%)	5 (10%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
HEMATOPOIESIS	2 (4%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(49)	(47)	(50)
NECROSIS, NOS	1 (2%)		
ANGIECTASIS			1 (2%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HEMATOPOIESIS	33 (67%)	32 (68%)	33 (66%)
#LYMPH NODE	(46)	(46)	(49)
MINERALIZATION		1 (2%)	
INFLAMMATION, NOS	1 (2%)	2 (4%)	
INFLAMMATION, GRANULOMATOUS		3 (7%)	
ANGIECTASIS	1 (2%)	4 (9%)	1 (2%)
HEMATOPOIESIS	15 (33%)	10 (22%)	6 (12%)
#LIVER	(49)	(50)	(50)
HEMATOPOIESIS	3 (6%)	1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#HEART	(49)	(49)	(49)
MINERALIZATION	1 (2%)	1 (2%)	
INFLAMMATION, NOS			1 (2%)
#MYOCARDIUM	(49)	(49)	(49)
DEGENERATION, NOS	4 (8%)	6 (12%)	1 (2%)
DIGESTIVE SYSTEM			
*INTESTINAL TRACT	(49)	(50)	(50)
METAPLASIA, NOS		1 (2%)	
#LIVER	(49)	(50)	(50)
MINERALIZATION		1 (2%)	1 (2%)
INFLAMMATION, NOS		1 (2%)	4 (8%)
FIBROSIS		1 (2%)	
DEGENERATION, NOS		40 (80%)	30 (60%)
NECROSIS, FOCAL	3 (6%)	5 (10%)	1 (2%)
NECROSIS, ISCHEMIC	1 (2%)	2 (4%)	
METAMORPHOSIS FATTY	4 (8%)	10 (20%)	4 (8%)
ANGIECTASIS			1 (2%)
*GALLBLADDER	(49)	(50)	(50)
INFLAMMATION, NOS			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, EPITHELIAL		4 (8%)	1 (2%)
#PANCREAS	(48)	(49)	(45)
INFLAMMATION, NOS		1 (2%)	
NECROSIS, NOS	1 (2%)		
#PANCREATIC ACINUS	(48)	(49)	(45)
ATROPHY, FOCAL		1 (2%)	
#STOMACH	(49)	(49)	(49)
INFLAMMATION, NOS	3 (6%)	2 (4%)	7 (14%)
NECROSIS, NOS	1 (2%)		2 (4%)
HYPERPLASIA, EPITHELIAL	1 (2%)	2 (4%)	
HYPERPLASIA, BASAL CELL			1 (2%)
HYPERKERATOSIS	6 (12%)	6 (12%)	11 (22%)
ACANTHOSIS		1 (2%)	3 (6%)
#PEYER'S PATCH	(45)	(46)	(46)
HYPERPLASIA, NOS	5 (11%)	2 (4%)	5 (11%)
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
MINERALIZATION	24 (49%)	28 (56%)	10 (20%)
INFLAMMATION, NOS	1 (2%)		
ABSCESS, NOS	1 (2%)		
NEPHROPATHY	18 (37%)	34 (68%)	36 (72%)
GLOMERULOSCLEROSIS, NOS	1 (2%)		
NECROSIS, NOS		1 (2%)	
#RENAL PAPILLA	(49)	(50)	(50)
MINERALIZATION	1 (2%)	2 (4%)	12 (24%)
#URINARY BLADDER	(49)	(49)	(47)
ABSCESS, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)
*PROSTATIC URETHRA	(49)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(43)	(39)
DILATATION, NOS		1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL	(48)	(49)	(49)
HYPERPLASIA, NOS	20 (42%)	21 (43%)	6 (12%)
#ADRENAL CORTEX	(48)	(49)	(49)
HYPERTROPHY, FOCAL	4 (8%)		1 (2%)
#ADRENAL MEDULLA	(48)	(49)	(49)
HYPERPLASIA, NOS	4 (8%)	7 (14%)	6 (12%)
#THYROID	(47)	(49)	(49)
FOLLICULAR CYST, NOS			2 (4%)
HYPERPLASIA, FOLLICULAR-CELL		3 (6%)	18 (37%)
#THYROID FOLLICLE	(47)	(49)	(49)
HYPERTROPHY, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*PENIS	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
NECROSIS, NOS	1 (2%)		
*PREPUTIAL GLAND	(49)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
HYPERKERATOSIS			1 (2%)
#TESTIS	(47)	(49)	(50)
MINERALIZATION		2 (4%)	
ATROPHY, NOS		1 (2%)	
#TESTIS/TUBULE	(47)	(49)	(50)
ATROPHY, FOCAL	5 (11%)	1 (2%)	1 (2%)
NERVOUS SYSTEM			
*CHOROID PLEXUS	(49)	(50)	(50)
MINERALIZATION		2 (4%)	
#BRAIN	(48)	(49)	(49)
MINERALIZATION	1 (2%)		
SPECIAL SENSE ORGANS			
*EAR	(49)	(50)	(50)
REACTION, FOREIGN BODY	1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*PENILE OR CLITORIDAL	(49)	(50)	(50)
HEMORRHAGE			1 (2%)
NECROSIS, NOS			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
ORBITAL REGION			
INFLAMMATION, NOS	1		
OMENTUM			
MINERALIZATION	1		
NECROSIS, FAT	2		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1
ANIMAL MISSING/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 ADMINISTERED DRINKING WATER CONTAINING 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

	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)
INFLAMMATION, NOS	1 (2%)	2 (4%)	1 (2%)
FIBROSIS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(49)
INFLAMMATION, NOS		1 (2%)	
#LUNG	(50)	(50)	(49)
HEMORRHAGE	1 (2%)	2 (4%)	
INFLAMMATION, NOS	1 (2%)	4 (8%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMATOPOIESIS	2 (4%)		1 (2%)
*ABDOMINAL CAVITY	(50)	(50)	(50)
HEMATOPOIESIS			1 (2%)
#BONE MARROW	(50)	(48)	(44)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)	1 (2%)	
#SPLEEN	(46)	(48)	(49)
MINERALIZATION			1 (2%)
NECROSIS, NOS			1 (2%)
ANGIECTASIS			2 (4%)
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	29 (63%)	32 (67%)	35 (71%)
#LYMPH NODE	(46)	(47)	(49)
HEMORRHAGE		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, GRANULOMATOUS		1 (2%)	
ANGIECTASIS		2 (4%)	
PLASMACYTOSIS		1 (2%)	
HEMATOPOIESIS	7 (15%)	1 (2%)	2 (4%)
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)	2 (4%)	2 (4%)
#ADRENAL	(50)	(49)	(47)
HEMATOPOIESIS			1 (2%)
CIRCULATORY SYSTEM			
#BRAIN	(50)	(50)	(49)
EMBOLUS, FAT			1 (2%)
#HEART	(50)	(50)	(49)
MINERALIZATION	1 (2%)		
INFLAMMATION, NOS	1 (2%)	1 (2%)	
#AURICULAR APPENDAGE	(50)	(50)	(49)
THROMBOSIS, NOS			1 (2%)
#MYOCARDIUM	(50)	(50)	(49)
DEGENERATION, NOS	4 (8%)	8 (16%)	3 (6%)
#UTERUS	(48)	(49)	(49)
THROMBOSIS, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*INTESTINAL TRACT	(50)	(50)	(50)
METAPLASIA, NOS			1 (2%)
#LIVER	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS			8 (16%)
DEGENERATION, NOS		1 (2%)	7 (14%)
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL	18 (36%)	20 (40%)	13 (26%)
NECROSIS, ISCHEMIC	1 (2%)		2 (4%)
METAMORPHOSIS FATTY	7 (14%)	12 (24%)	6 (12%)
FOCAL CELLULAR CHANGE		4 (8%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
EOSINOPHILIC CYTO CHANGE		1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)		
#LIVER/HEPATOCYTES	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	
*GALLBLADDER	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL		2 (4%)	6 (12%)
#PANCREAS	(48)	(44)	(46)
INFLAMMATION, NOS			1 (2%)
#PANCREATIC ACINUS	(48)	(44)	(46)
ATROPHY, NOS	2 (4%)	1 (2%)	2 (4%)
#STOMACH	(50)	(49)	(48)
MINERALIZATION	2 (4%)	1 (2%)	
INFLAMMATION, NOS	6 (12%)	8 (16%)	4 (8%)
NECROSIS, NOS	2 (4%)	4 (8%)	1 (2%)
HYPERPLASIA, EPITHELIAL	2 (4%)		
HYPERKERATOSIS	18 (36%)	17 (35%)	19 (40%)
ACANTHOSIS	8 (16%)	8 (16%)	6 (13%)
METAPLASIA, SQUAMOUS			1 (2%)
#PEYER'S PATCH	(45)	(47)	(46)
HYPERPLASIA, NOS	6 (13%)		4 (9%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION	2 (4%)	8 (16%)	8 (16%)
INFLAMMATION, INTERSTITIAL			1 (2%)
NEPHROPATHY	6 (12%)	21 (42%)	35 (70%)
GLOMERULOSCLEROSIS, NOS		1 (2%)	
#RENAL PAPILLA	(50)	(50)	(50)
MINERALIZATION	1 (2%)	1 (2%)	14 (28%)
#KIDNEY/TUBULE	(50)	(50)	(50)
NECROSIS, FOCAL			1 (2%)
#URINARY BLADDER	(49)	(48)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(42)	(40)	(39)
DILATATION, NOS			2 (5%)
HYPERPLASIA, NOS			1 (3%)
HYPERPLASIA, FOCAL	2 (5%)	2 (5%)	
#ADRENAL	(50)	(49)	(47)
DILATATION, NOS		1 (2%)	
DEGENERATION, CYSTIC	1 (2%)		
METAMORPHOSIS FATTY	1 (2%)		
HYPERPLASIA, NOS	36 (72%)	39 (80%)	38 (81%)
#ADRENAL CORTEX	(50)	(49)	(47)
HYPERTROPHY, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(50)	(49)	(47)
HYPERPLASIA, NOS	2 (4%)	1 (2%)	2 (4%)
#THYROID	(50)	(47)	(50)
FOLLICULAR CYST, NOS	1 (2%)		
INFLAMMATION, NECROTIZING	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL			23 (46%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE			1 (2%)
#UTERUS	(48)	(49)	(49)
HYDROMETRA	19 (40%)	11 (22%)	12 (24%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS			2 (4%)
ABSCESS, NOS			1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
#UTERUS/ENDOMETRIUM	(48)	(49)	(49)
HYPERPLASIA, NOS			3 (6%)
HYPERPLASIA, CYSTIC	28 (58%)	29 (59%)	23 (47%)
#OVARY	(43)	(38)	(34)
MINERALIZATION		2 (5%)	2 (6%)
INFLAMMATION, NOS			1 (3%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
*CHOROID PLEXUS	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
INFLAMMATION, NOS			1 (2%)
ABSCESS, NOS	1 (2%)		
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
SITE UNKNOWN			
HEMORRHAGE			1
OMENTUM			
NECROSIS, FAT	1	1	1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		

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

APPENDIX E

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

TABLE E1. HISTORICAL INCIDENCE OF THYROID FOLLICULAR CELL TUMORS IN UNTREATED CONTROL MALE F344/N RATS *(a)*

Laboratory	Follicular Cell Adenoma	Follicular Cell Carcinoma	Follicular Cell Adenoma or Carcinoma
Battelle	4/287 (1.4%)	3/287 (1.0%)	7/287 (2.4%)
Dow	0/89 (0.0%)	2/89 (2.2%)	2/89 (2.2%)
Frederick	2/462 (0.4%)	4/462 (0.9%)	6/462 (1.3%)
Gulf South	2/93 (2.2%)	2/93 (2.2%)	4/93 (4.3%)
Hazleton	2/192 (1.0%)	1/192 (0.5%)	3/192 (1.6%)
Litton	3/703 (0.4%)	4/703 (0.6%)	7/703 (1.0%)
Mason (b)	3/989 (0.3%)	3/989 (0.3%)	6/989 (0.6%)
Papanicolaou	2/44 (4.6%)	0/44 (0.0%)	2/44 (4.6%)
Southern	8/584 (1.4%)	6/584 (1.0%)	14/584 (2.4%)
Total	26/3443 (0.8%)	25/3443 (0.7%)	51/3443 (1.5%)
Overall Historical Range			
High	2/49 (4.0%)	1/37 (3.0%)	4/89 (4.5%)
Low	0/53 (0.0%)	0/53 (0.0%)	0/53 (0.0%)
Current Study			
Control	1/49 (2.0%)	0/49 (0.0%)	1/49 (2.0%)
Low-dose	4/47 (8.5%)	0/47 (0.0%)	4/47 (8.5%)
High-dose	3/48 (6.2%)	7/48 (14.5%)	10/48 (20.8%)

(a) Data as of June 15, 1981. The range is presented for groups of 35 or more animals.
(b) Historical data include the control data from this study.

TABLE E2. HISTORICAL INCIDENCE OF THYROID C-CELL TUMORS IN UNTREATED CONTROL FEMALE F344/N RATS *(a)*

Laboratory	C-Cell Adenoma	C-Cell Carcinoma	C-Cell Adenoma or Carcinoma
Battelle	2/281 (0.7%)	10/281 (3.6%)	12/281 (4.3%)
Dow	11/98 (11.2%)	2/98 (2.0%)	13/98 (13.3%)
Frederick	41/519 (7.9%)	10/519 (1.9%)	51/519 (9.8%)
Gulf South	9/92 (9.8%)	1/92 (1.1%)	10/92 (10.9%)
Hazleton	4/196 (2.0%)	3/196 (1.5%)	7/196 (3.6%)
Litton	32/689 (4.6%)	14/689 (2.0%)	45/689 (6.5%)
Mason (b)	28/1056 (2.7%)	35/1056 (3.3%)	63/1056 (6.0%)
Papanicolaou	2/36 (5.6%)	1/36 (2.8%)	3/36 (8.3%)
Southern	50/577 (8.7%)	22/577 (3.8%)	69/577 (12.0%)
Total	179/3544 (5.1%)	98/3544 (2.8%)	273/3544 (7.7%)
Overall Historical Range			
High	9/52 (17.3%)	5/50 (10.0%)	13/52 (25.0%)
Low	0/86 (0.0%)	0/50 (0.0%)	0/50 (0.0%)
Current Study			
Control	0/47 (0.0%)	1/47 (2.1%)	1/47 (2.1%)
Low-dose	3/47 (6.3%)	2/47 (4.2%)	5/47 (10.6%)
High-dose	6/48 (12.5%)	1/48 (2.0%)	7/48 (14.5%)

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

(b) Historical data include control data from this study.

TABLE E3. HISTORICAL INCIDENCE OF THYROID FOLLICULAR CELL TUMORS IN UNTREATED CONTROL FEMALE F344/N RATS *(a)*

	Follicular Adenoma	Follicular Carcinoma	F-Cell Adenoma or Carcinoma
Battelle	1/281 (0.4%)	1/281 (0.4%)	2/281 (0.7%)
Dow	1/98 (1.0%)	2/98 (2.0%)	3/98 (3.1%)
Frederick	1/519 (0.2%)	5/519 (1.0%)	6/519 (1.2%)
Gulf South	0/92 (0.0%)	1/92 (1.1%)	1/92 (1.1%)
Hazleton	1/196 (0.5%)	0/196 (0.0%)	1/196 (0.5%)
Litton	1/689 (0.1%)	0/689 (0.0%)	1/689 (0.1%)
Mason (b)	1/1056 (0.1%)	5/1056 (0.5%)	6/1056 (0.6%)
Papanicolaou	0/36 (0.0%)	0/36 (0.0%)	0/36 (0.0%)
Southern	4/577 (0.7%)	1/577 (0.2%)	5/577 (0.9%)
Total	10/3544 (0.3%)	15/3544 (0.4%)	25/3544 (0.7%)
Overall Historical Range			
High	1/42 (2.3%)	1/40 (2.5%)	2/48 (4.2%)
Low	0/52 (0.0%)	0/86 (0.0%)	0/50 (0.0%)
Current Study			
Control	0/47 (0.0%)	0/47 (0%)	0/47 (0.0%)
Low-dose	2/47 (4.3%)	2/47 (4.3%)	4/47 (8.5%)
High-dose	17/48 (35.4%)	2/48 (4.2%)	19/48 (39.5%)

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

(b) Historical data include control data from this study.

TABLE E4. HISTORICAL INCIDENCE OF LIVER TUMORS IN UNTREATED CONTROL MALE F344/N RATS *(a)*

Laboratory	Neoplastic Nodule	Carcinoma	Combined
Battelle	13/288 (4.5%)	4/288 (1.4%)	17/288 (5.9%)
Dow	0/98 (0.0%)	0/98 (0.0%)	0/98 (0.0%)
Frederick	5/465 (1.1%)	5/465 (1.1%)	10/465 (2.2%)
Gulf South	1/95 (1.1%)	0/95 (0.0%)	1/95 (1.1%)
Hazleton	3/196 (1.5%)	3/196 (1.5%)	6/196 (3.1%)
Litton	14/779 (1.8%)	4/779 (0.5%)	18/779 (2.3%)
Mason *(b)*	20/1058 (1.9%)	7/1058 (0.7%)	27/1058 (2.6%)
Papanicolaou	1/49 (2.0%)	0/49 (0.0%)	1/49 (2.0%)
Southern	10/590 (1.7%)	1/590 (0.2%)	11/590 (1.9%)
Total	67/3618 (1.9%)	24/3618 (0.7%)	91/3618 (2.5%)
Overall Historical Range			
High	5/47 (10.6%)	2/48 (4.2%)	6/50 (16.0%)
Low	0/54 (0.0%)	0/90 (0.0%)	0/50 (0.0%)
Current Study			
Control	1/50 (2.0%)	0/50 (0.0%)	1/50 (2.0%)
Low-dose	12/50 (24.0%)	1/50 (2.0%)	13/50 (26.0%)
High-dose	25/50 (50.0%)	1/50 (2.0%)	25/50 (50.0%)

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

(b) Historical data include control data from this study.

TABLE E5. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN UNTREATED CONTROL MALE F344/N RATS *(a)*

Laboratory	Leukemia	Leukemia or Lymphoma
Battelle	84/290 (29.0%)	90/290 (31.0%)
Dow	9/100 (9.0%)	28/100 (28.0%)
Frederick	59/467 (12.6%)	119/467 (25.5%)
Gulf South	28/97 (28.9%)	29/97 (29.9%)
Hazleton	49/198 (24.7%)	52/198 (26.3%)
Litton	115/789 (14.6%)	126/789 (16.0%)
Mason *(b)*	207/1066 (19.4%)	238/1066 (22.3%)
Papanicolaou	10/50 (10.0%)	11/50 (12.0%)
Southern	123/591 (20.8%)	137/591 (23.2%)
Total	684/3648 (18.7%)	830/3648 (22.8%)
Overall Historical Range		
High	23/50 (46.0%)	27/50 (54.0%)
Low	0/50 (0.0%)	2/46 (4.5%)
Current Study		
Control	12/50 (24.0%)	12/50 (24.0%)
Low-dose	6/50 (12.0%)	7/50 (14.0%)
High-dose	5/50 (10.0%)	5/50 (10.0%)

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

(b) Historical data include control data from this study.

TABLE E6. HISTORICAL INCIDENCE OF GRANULOSA CELL TUMORS OR CARCINOMAS OF THE OVARY IN UNTREATED CONTROL FEMALE F344/N RATS *(a)*

Laboratory	Granulosa Cell Tumors	Granulosa Cell Carcinomas
Battelle	0/288	0/288
Dow	0/99	0/99
Frederick	1/518 (0.19%)	0/518
Gulf South	0/100	0/100
Hazleton	0/200	0/200
Litton	3/715 (0.42%)	0/715
Mason *(b)*	6/1081 (0.56%)	1/1081 (0.09%)
Papanicolaou	0/49	0/49
Southern	1/592 (0.17%)	0/592
Total	11/3642 (0.31%)	1/3642 (0.03%)
Current Study		
Control	0/50 (0.0%)	0/50 (0.0%)
Low-dose	3/50 (6.0%)	1/50 (2.0%)
High-dose	2/50 (4.0%)	0/50 (0.0%)

(a) Data as of June 15, 1981 for studies of at least 104 weeks.
(b) Historical data include control data from this study.

TABLE E7. HISTORICAL INCIDENCE OF TRANSITIONAL CELL PAPILLOMAS AND CARCINOMAS OF THE URINARY BLADDER IN UNTREATED CONTROL FEMALE F344/N RATS *(a)*

Laboratory	Papillomas	Carcinomas
Battelle	0/288	0/288
Dow	0/77	1/77 (1.30%)
Frederick	0/505	1/505 (0.2%)
Gulf South	0/100	0/100
Harleton	0/200	0/200
Litton	0/756	0/756
Mason *(b)*	2/1078 (0.19%)	1/1078 (0.09%)
Papanicolaou	0/49	0/49
Southern	1/591 (0.17%)	1/591 (0.17%)
Total	3/3644 (0.08%)	4/3644 (0.11%)
Current Study		
Control	0/48 (0.0%)	0/48 (0.0%)
Low-dose	2/50 (4.0%)	0/50 (0.0%)
High-dose	1/50 (2.0%)	0/50 (0.0%)

(a) Data as of June 15, 1981 for studies of at least 104 weeks.
(b) Historical data include control data from this study.

TABLE E8. HISTORICAL INCIDENCE OF THYROID FOLLICULAR CELL TUMORS IN UNTREATED CONTROL MALE B6C3F$_1$ MICE *(a)*

Laboratory	Follicular Cell Adenoma	Follicular Cell Carcinoma	Follicular Cell Adenoma or Carcinoma
Battelle	2/336 (0.6%)	0/336 (0.0%)	2/336 (0.6%)
Dow	1/82 (1.2%)	1/82 (1.2%)	2/82 (2.4%)
Frederick	2/393 (0.5%)	2/393 (0.5%)	4/393 (1.0%)
Gulf South	1/44 (2.3%)	1/44 (2.3%)	2/44 (4.5%)
Hazleton	0/47 (0.0%)	0/47 (0.0%)	0/47 (0.0%)
Litton	3/398 (0.8%)	0/398 (0.0%)	3/398 (0.8%)
Mason *(b)*	3/787 (0.4%)	2/787 (0.3%)	5/787 (0.6%)
Southern	13/607 (2.1%)	0/607 (0.0%)	13/607 (2.1%)
Total	25/2694 (0.9%)	6/2694 (0.2%)	31/2694 (1.2%)
Overall Historical Range			
High	3/49 (6.1%)	1/39 (2.5%)	3/49 (6.1%)
Low	0/50 (0.0%)	0/48 (0.0%)	0/50 (0.0%)
Current Study			
Control	0/47 (0.0%)	0/47 (0.0%)	0/47 (0.0%)
Low-dose	3/49 (6.1%)	0/49 (0.0%)	3/49 (6.1%)
High-dose	16/49 (32.7%)	0/49 (0.0%)	16/49 (32.7%)

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

(b) Historical data include control data from this study.

TABLE E9. HISTORICAL INCIDENCE OF THYROID FOLLICULAR CELL TUMORS IN UNTREATED CONTROL FEMALE B6C3F$_1$ MICE *(a)*

Laboratory	Follicular Cell Adenoma	Follicular Cell Carcinoma	Follicular Cell Adenoma or Carcinoma
Battelle	2/339 (0.6%)	1/339 (0.3%)	3/339 (0.9%)
Dow	1/78 (1.3%)	0/78 (0.0%)	1/78 (1.3%)
Frederick	12/424 (2.8%)	1/424 (0.2%)	13/424 (3.1%)
Gulf South	1/54 (1.9%)	2/54 (3.7%)	3/54 (5.6%)
Hazleton	2/94 (2.1%)	0/94 (0.0%)	2/94 (2.1%)
Litton	9/384 (2.3%)	1/384 (0.3%)	10/384 (2.6%)
Mason *(b)*	10/787 (1.3%)	3/787 (0.4%)	13/787 (1.7%)
Southern	12/609 (2.0%)	2/609 (0.3%)	14/609 (2.3%)
Total	49/2769 (1.8%)	10/2769 (0.4%)	59/2769 (2.1%)
Overall Historical Range			
High	2/44 (4.5%)	2/44 (4.5%)	4/44 (9.1%)
Low	0/50 (0.0%)	0/49 (0.0%)	0/50 (0.0%)
Current Study			
Control	0/50 (0.0%)	0/50 (0.0%)	0/50 (0.0%)
Low-dose	1/47 (2.1%)	0/47 (0.0%)	1/47 (2.1%)
High-dose	13/50 (26.0%)	2/50 (4.0%)	15/50 (30.0%)

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

(b) Historical data include control data from this study.

TABLE E10. HISTORICAL INCIDENCE OF LIVER TUMORS IN UNTREATED CONTROL MALE $B6C3F_1$ MICE *(a)*

Laboratory	Adenoma	Carcinoma	Adenoma or Carcinoma
Battelle	30/347 (8.6%)	75/347 (21.6%)	102/347 (29.4%)
Dow	13/98 (13.3%)	33/98 (33.7%)	46/98 (46.9%)
Frederick	31/407 (7.6%)	100/407 (24.6%)	131/407 (32.2%)
Gulf South	4/48 (8.3%)	13/48 (27.1%)	16/48 (33.3%)
Hazleton	3/49 (6.1%)	17/49 (34.7%)	20/49 (40.8%)
Litton	47/499 (9.4%)	85/499 (17.0%)	132/499 (26.5%)
Mason *(b)*	77/849 (9.1%)	209/849 (24.6%)	281/849 (33.1%)
Southern	65/635 (10.2%)	114/635 (18.0%)	177/635 (27.9%)
Total	270/2932 (9.2%)	646/2932 (22.0%)	905/2932 (30.9%)
Overall Historical Range			
High	11/50 (22.0%)	24/54 (44.4%)	29/50 (58.0%)
Low	0/49 (0.0%)	4/50 (8.0%)	8/50 (16.0%)
Current Study			
Control	7/49 (14.3%)	10/49 (20.4%)	17/49 (34.7%)
Low-dose	10/50 (20.0%)	33/50 (66.0%)	43/50 (86.0%)
High-dose	8/50 (16.0%)	29/50 (58.0%)	37/50 (74.0%)

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

(b) Historical data include control data from this study.

TABLE E11. HISTORICAL INCIDENCE OF LIVER TUMORS IN UNTREATED CONTROL FEMALE B6C3F1 MICE *(a)*

Laboratory	Adenoma	Carcinoma	Combined
Battelle	5/348 (1.4%)	21/348 (6.0%)	25/348 (7.2%)
Dow	3/98 (3.1%)	5/98 (5.1%)	7/98 (7.1%)
Frederick	10/431 (2.3%)	13/431 (3.0%)	22/431 (5.1%)
Gulf South	8/134 (6.0%)	5/134 (3.7%)	13/134 (9.7%)
Hazleton	1/100 (1.0%)	4/100 (4.0%)	5/100 (5.0%)
Litton	21/512 (4.1%)	11/512 (2.1%)	32/512 (6.3%)
Mason *(b)*	38/859 (4.4%)	40/859 (4.7%)	77/859 (9.0%)
Southern	18/645 (2.8%)	21/645 (3.3%)	38/645 (5.9%)
Total	104/3127 (3.3%)	120/3127 (3.8%)	219/3127 (7.0%)
Overall Historical Range			
High	9/49 (18.4%)	7/49 (14.2%)	10/49 (20.4%)
Low	0/50 (0.0%)	0/50 (0.0%)	0/50 (0.0%)
Current Study			
Control	3/50 (6.0%)	1/50 (2.0%)	4/50 (8.0%)
Low-dose	9/50 (18.0%)	6/50 (12.0%)	15/50 (30.0%)
High-dose	12/50 (24.0%)	11/50 (22.0%)	23/50 (46.0%)

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

(b) Historical data include control data from this study.

TABLE E12. HISTORICAL INCIDENCE OF ADRENAL TUMORS IN UNTREATED CONTROL MALE $B6C3F_1$ MICE *(a)*

Laboratory	Pheochromocytoma
Battelle	2/340 (0.6%)
Dow	2/93 (2.2%)
Frederick	1/402 (0.3%)
Gulf South	3/47 (6.4%)
Hazleton	0/49 (0.0%)
Litton	5/446 (1.1%)
Mason *(b)*	6/793 (0.8%)
Southern	2/623 (0.3%)
Total	21/2793 (0.8%)
Overall Historical Range	
High	3/47 (6.4%)
Low	0/50 (0.0%)
Current Study	
Control	2/48 (4.2%)
Low-dose	12/49 (24.5%)
High-dose	14/49 (28.6%)

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

(b) Historical data include control data from this study.

TABLE E13. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN UNTREATED CONTROL FEMALE B6C3F$_1$ MICE *(a)*

Laboratory	Lymphoma	Lymphoma or Leukemia
Battelle	76/350 (21.7%)	84/350 (24.0%)
Dow	38/99 (38.4%)	41/99 (41.4%)
Frederick	97/435 (22.3%)	100/435 (23.0%)
Gulf South	22/137 (16.1%)	47/137 (34.3%)
Hazleton	25/100 (25.0%)	26/100 (26.0%)
Litton	118/513 (23.0%)	134/513 (26.1%)
Mason *(b)*	253/867 (29.2%)	260/867 (30.0%)
Southern	117/652 (17.9%)	131/652 (20.1%)
Total	746/3153 (23.7%)	823/3153 (26.1%)
Overall Historical Range		
High	31/50 (62.0%)	30/48 (62.5%)
Low	4/50 (8.0%)	4/50 (8.0%)
Current Study		
Control	13/50 (26.0%)	13/50 (26.0%)
Low-dose	28/50 (56.0%)	28/50 (56.0%)
High-dose	29/50 (58.0%)	29/50 (58.0%)

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

(b) Historical data include control data from this study.

TABLE E14. HISTORICAL INCIDENCE OF LUNG TUMORS IN UNTREATED CONTROL MALE B6C3F1 MICE *(a)*

Laboratory	Alveolar/ Bronchiolar Adenoma	Alveolar/ Bronchiolar Carcinoma	Alveolar/ Bronchiolar Adenoma or Carcinoma
Battelle	22/393 (6.4%)	6/343 (1.8%)	28/343 (8.2%)
Dow	15/99 (15.2%)	8/99 (8.1%)	23/99 (23.2%)
Frederick	40/407 (9.8%)	50/407 (12.3%)	89/407 (21.9%)
Gulf South	0/47 (0%)	1/47 (2.1%)	1/47 (2.1%)
Hazleton	8/49 (16.3%)	1/49 (2.0%)	9/49 (18.3%)
Litton	62/497 (12.5%)	24/497 (4.8%)	86/497 (17.3%)
Mason *(b)*	129/847 (15.2%)	60/847 (7.1%)	186/847 (22.0%)
Southern	61/636 (9.6%)	43/636 (6.8%)	101/636 (15.9%)
Total	337/2925 (11.5%)	193/2925 (6.6%)	523/2925 (17.9%)
Overall Historical Range			
High	14/50 (28.0%)	8/48 (16.6%)	17/50 (34.0%)
Low	0/47 (0.0%)	0/50 (0.0%)	1/49 (2.0%)
Current Study			
Control	12/49 (24.5%)	1/49 (2.0%)	13/49 (26.5%)
Low-dose	9/49 (18.4%)	4/49 (8.2%)	12/49 (24.5%)
High-dose	3/49 (6.1%)	1/49 (2.0%)	4/49 (8.2%)

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

(b) Historical data include control data from this study.

TABLE E15. HISTORICAL INCIDENCE OF LUNG TUMORS IN UNTREATED CONTROL FEMALE B6C3F$_1$ MICE *(a)*

Laboratory	Alveolar/ Bronchiolar Adenoma	Alveolar/ Bronchiolar Carcinoma	Alveolar/ Bronchiolar Adenoma *or* Carcinoma
Battelle	13/349 (3.7%)	5/349 (1.4%)	18/349 (5.2%)
Dow	5/95 (5.3%)	1/95 (1.1%)	6/95 (6.3%)
Frederick	18/428 (4.2%)	11/428 (2.6%)	29/428 (6.8%)
Gulf South	3/64 (4.7%)	4/64 (6.3%)	7/64 (10.9%)
Hazleton	5/99 (5.1%)	1/99 (1.0%)	6/99 (6.1%)
Litton	25/502 (5.0%)	4/502 (0.8%)	29/502 (5.8%)
Mason *(b)*	53/864 (6.1%)	21/864 (2.4%)	74/864 (8.6%)
Southern	29/645 (4.5%)	11/645 (1.7%)	39/645 (6.0%)
Total	151/3046 (5.0%)	58/3046 (1.9%)	208/3046 (6.8%)
Overall Historical Range			
High	7/50 (14.0%)	4/48 (8.3%)	8/50 (16.0%)
Low	0/50 (0.0%)	0/50 (0.0%)	0/50 (0.0%)
Current Study			
Control	1/50 (2.0%)	1/50 (2.0%)	2/50 (4.0%)
Low-dose	2/50 (4.0%)	1/50 (2.0%)	3/50 (6.0%)
High-dose	6/49 (12.2%)	2/49 (4.1%)	8/49 (16.3%)

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

(b) Historical data include control data from this study.

APPENDIX F

ANALYSIS OF PRIMARY TUMORS IN F344/N RATS AND B6C3F$_1$ MICE

TABLE K1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)*

	Control	Low Dose	High Dose
Skin: Squamous Cell Papilloma			
Tumor Rates			
Overall *(b)*	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted *(c)*	0.0%	9.8%	2.5%
Terminal *(d)*	0/38 (0%)	4/41 (10%)	1/40 (3%)
Statistical Tests *(e)*			
Life Table	P=0.408	P=0.073	P=0.510
Incidental Tumor Test	P=0.408	P=0.073	P=0.510
Cochran-Armitage Trend Test	P=0.390		
Fisher Exact Test		P=0.059	P=0.500
Skin: Squamous Cell Papilloma or Carcinoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted *(c)*	2.6%	9.8%	2.5%
Terminal *(d)*	1/38 (3%)	4/41 (10%)	1/40 (3%)
Statistical Tests *(e)*			
Life Table	P=0.581N	P=0.203	P=0.750N
Incidental Tumor Test	P=0.581N	P=0.203	P=0.750N
Cochran-Armitage Trend Test	P=0.601		
Fisher Exact Test		P=0.181	P=0.753
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(b)*	5/50 (10%)	1/50 (2%)	2/50 (4%)
Adjusted *(c)*	12.6%	2.3%	5.0%
Terminal *(d)*	4/38 (11%)	0/41 (0%)	2/40 (5%)
Statistical Tests *(e)*			
Life Table	P=0.116N	P=0.089N	P=0.196N
Incidental Tumor Test	P=0.107N	P=0.105N	P=0.185N
Cochran-Armitage Trend Test	P=0.133N		
Fisher Exact Test		P=0.102N	P=0.218N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted *(c)*	5.3%	7.3%	9.7%
Terminal *(d)*	2/38 (5%)	3/41 (7%)	3/40 (8%)
Statistical Tests *(e)*			
Life Table	P=0.288	P=0.535	P=0.368
Incidental Tumor Test	P=0.298	P=0.535	P=0.380
Cochran-Armitage Trend Test	P=0.264		
Fisher Exact Test		P=0.500	P=0.339
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	3/50 (6%)	5/50 (10%)
Adjusted *(c)*	5.3%	7.3%	12.1%
Terminal *(d)*	2/38 (5%)	3/41 (7%)	4/40 (10%)
Statistical Tests *(e)*			
Life Table	P=0.176	P=0.535	P=0.244
Incidental Tumor Test	P=0.184	P=0.535	P=0.253
Cochran-Armitage Trend Test	P=0.158		
Fisher Exact Test		P=0.500	P=0.218

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Hematopoietic System: Myelomonocytic Leukemia			
Tumor Rates			
Overall *(b)*	9/50 (18%)	6/50 (12%)	5/50 (10%)
Adjusted *(c)*	21 9%	14 6%	11 8%
Terminal *(d)*	7/38 (18%)	6/41 (15%)	3/40 (8%)
Statistical Tests *(e)*			
Life Table	P=0 129N	P=0 242N	P=0 169N
Incidental Tumor Test	P=0 136N	P=0 270N	P=0 180N
Cochran-Armitage Trend Test	P=0 152N		
Fisher Exact Test		P=0 288N	P=0 194N
Hematopoietic System: Leukemia			
Tumor Rates			
Overall *(b)*	12/50 (24%)	6/50 (12%)	5/50 (10%)
Adjusted *(c)*	27 9%	14 6%	11 8%
Terminal *(d)*	8/38 (21%)	6/41 (15%)	3/40 (8%)
Statistical Tests *(e)*			
Life Table	P=0 029N	P=0 077N	P=0 048N
Incidental Tumor Test	P=0 036N	P=0 103N	P=0 059N
Cochran-Armitage Trend Test	P=0 036N		
Fisher Exact Test		P=0 096N	P=0 054N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	12/50 (24%)	7/50 (14%)	5/50 (10%)
Adjusted *(c)*	27 9%	16 5%	11 8%
Terminal *(d)*	8/38 (21%)	6/41 (15%)	3/40 (8%)
Statistical Tests *(e)*			
Life Table	P=0 032N	P=0 127N	P=0 048N
Incidental Tumor Test	P=0 046N	P=0 173N	P=0 059N
Cochran-Armitage Trend Test	P=0 038N		
Fisher Exact Test		P=0 154N	P=0 054N
Liver: Neoplastic Nodule			
Tumor Rates			
Overall *(b)*	1/50 (2%)	12/50 (24%)	25/50 (50%)
Adjusted *(c)*	2 6%	29 3%	56 6%
Terminal *(d)*	1/38 (3%)	12/41 (29%)	21/40 (53%)
Statistical Tests *(e)*			
Life Table	P<0 001	P=0 002	P<0 001
Incidental Tumor Test	P<0 001	P=0 002	P<0 001
Cochran-Armitage Trend Test	P<0 001		
Fisher Exact Test		P=0 001	P<0 001
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	24/46 (52%)	20/47 (43%)	21/49 (43%)
Adjusted *(c)*	59 3%	45 9%	47 3%
Terminal *(d)*	20 36 (56%)	15/38 (39%)	17/40 (43%)
Statistical Tests *(e)*			
Life Table	P=0 180N	P=0 207N	P=0 204N
Incidental Tumor Test	P=0 196N	P=0 225N	P=0 267N
Cochran-Armitage Trend Test	P=0 212N		
Fisher Exact Test		P=0 235N	P=0 241N

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Adrenal: All Pheochromocytomas			
Tumor Rates			
Overall *(b)*	8/50 (16%)	5/49 (10%)	5/49 (10%)
Adjusted *(c)*	20.1%	12.1%	12.5%
Terminal *(d)*	7/38 (18%)	4/40 (10%)	5/40 (13%)
Statistical Tests *(e)*			
Life Table	P=0.191N	P=0.246N	P=0.245N
Incidental Tumor Test	P=0.221N	P=0.279N	P=0.293N
Cochran-Armitage Trend Test	P=0.232N		
Fisher Exact Test		P=0.290N	P=0.290N
Thyroid: Follicular Cell Adenoma			
Tumor Rates			
Overall *(b)*	1/49 (2%)	4/47 (9%)	3/48 (6%)
Adjusted *(c)*	2.6%	9.4%	7.1%
Terminal *(d)*	1/38 (3%)	2/40 (5%)	2/40 (5%)
Statistical Tests *(e)*			
Life Table	P=0.293	P=0.208	P=0.338
Incidental Tumor Test	P=0.264	P=0.166	P=0.321
Cochran-Armitage Trend Test	P=0.245		
Fisher Exact Test		P=0.168	P=0.301
Thyroid: Follicular Cell Carcinoma			
Tumor Rates			
Overall *(b)*	0/49 (0%)	0/47 (0%)	7/48 (15%)
Adjusted *(c)*	0.0%	0.0%	17.0%
Terminal *(d)*	0/38 (0%)	0/40 (0%)	6/40 (15%)
Statistical Tests *(e)*			
Life Table	P=0.001	*(f)*	P=0.012
Incidental Tumor Test	P=0.001	*(f)*	P=0.011
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		*(f)*	P=0.006
Thyroid: Follicular Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	1/49 (2%)	4/47 (9%)	10/48 (21%)
Adjusted *(c)*	2.6%	9.4%	23.6%
Terminal *(d)*	1/38 (3%)	2/40 (5%)	8/40 (20%)
Statistical Tests *(e)*			
Life Table	P=0.004	P=0.208	P=0.008
Incidental Tumor Test	P=0.003	P=0.166	P=0.007
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.168	P=0.003
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/49 (6%)	2/47 (4%)	2/48 (4%)
Adjusted *(c)*	7.9%	5.0%	5.0%
Terminal *(d)*	3/38 (8%)	2/40 (5%)	2/40 (5%)
Statistical Tests *(e)*			
Life Table	P=0.384N	P=0.477N	P=0.477N
Incidental Tumor Test	P=0.384N	P=0.477N	P=0.477N
Cochran-Armitage Trend Test	P=0.416N		
Fisher Exact Test		P=0.520N	P=0.510N

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Pancreatic Islets: Islet Cell Adenoma			
Tumor Rates			
Overall *(b)*	2/49 (4%)	4/49 (8%)	3/47 (6%)
Adjusted *(c)*	5 1%	9 5%	6 6%
Terminal *(d)*	1/38 (3%)	3/40 (8%)	1/40 (3%)
Statistical Tests *(e)*			
Life Table	P=0 458	P=0.370	P=0 546
Incidental Tumor Test	P=0 387	P=0 325	P=0 458
Cochran-Armitage Trend Test	P=0 396		
Fisher Exact Test		P=0 339	P=0.480
Preputial Gland: Adenoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted *(c)*	7 6%	0.0%	2 5%
Terminal *(d)*	2/38 (5%)	0/41 (0%)	1/40 (3%)
Statistical Tests *(e)*			
Life Table	P=0.162N	P=0.109N	P=0 283N
Incidental Tumor Test	P=0 155N	P=0 124N	P=0 268N
Cochran-Armitage Trend Test	P=0 176N		
Fisher Exact Test		P=0 121N	P=0.309N
Preputial Gland: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	4/50 (8%)	0/50 (0%)	3/50 (6%)
Adjusted *(c)*	10 1%	0 0%	6.8%
Terminal *(d)*	3/38 (8%)	0/41 (0%)	1/40 (3%)
Statistical Tests *(e)*			
Life Table	P=0 370N	P=0.055N	P=0 452N
Incidental Tumor Test	P=0 338N	P=0.063N	P=0.416N
Cochran-Armitage Trend Test	P=0 406N		
Fisher Exact Test		P=0.059N	P=0.500N
Testis: All Interstitial Cell Tumors			
Tumor Rates			
Overall *(b)*	42/49 (86%)	42/50 (84%)	48/50 (96%)
Adjusted *(c)*	91 3%	95.4%	100.0%
Terminal *(d)*	34/38 (89%)	39/41 (95%)	40/40 (100%)
Statistical Tests *(e)*			
Life Table	P=0 239	P=0.295N	P=0.310
Incidental Tumor Test	P=0.142	P=0 396N	P=0.171
Cochran-Armitage Trend Test	P=0.072		
Fisher Exact Test		P=0 517N	P=0 075

(a) Dosed groups received doses of 150 or 300 ppm of 4,4'-methylenedianiline as the dihydrochloride in the drinking water

(b) Number of tumor bearing animals/ number of animals examined at the site

(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

(d) Observed tumor incidence at terminal kill

(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N)

(f) Not significant No tumors observed in control or dosed groups

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)*

	Control	Low Dose	High Dose
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted *(c)*	2.2%	0.0%	6.6%
Terminal *(d)*	0/38 (0%)	0/35 (0%)	2/43 (5%)
Statistical Tests *(e)*			
Life Table	P=0.201	P=0.509N	P=0.339
Incidental Tumor Test	P=0.238	P=0.154N	P=0.529
Cochran-Armitage Trend Test	P=0.176		
Fisher Exact Test		P=0.500N	P=0.309
Skin or Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted *(c)*	4.7%	0.0%	6.6%
Terminal *(d)*	1/38 (3%)	0/35 (0%)	2/43 (5%)
Statistical Tests *(e)*			
Life Table	P=0.428	P=0.254N	P=0.543
Incidental Tumor Test	P=0.507	P=0.085N	P=0.660N
Cochran-Armitage Trend Test	P=0.390		
Fisher Exact Test		P=0.247N	P=0.500
Hematopoietic System: Myelomonocytic Leukemia			
Tumor Rates			
Overall *(b)*	3/50 (6%)	7/50 (14%)	2/50 (4%)
Adjusted *(c)*	7.1%	18.0%	4.2%
Terminal *(d)*	1/38 (3%)	4/35 (11%)	0/43 (0%)
Statistical Tests *(e)*			
Life Table	P=0.386N	P=0.141	P=0.467N
Incidental Tumor Test	P=0.527	P=0.093	P=0.703N
Cochran-Armitage Trend Test	P=0.427N		
Fisher Exact Test		P=0.159	P=0.500N
Liver: Neoplastic Nodule			
Tumor Rates			
Overall *(b)*	4/50 (8%)	8/50 (16%)	8/50 (16%)
Adjusted *(c)*	10.5%	20.8%	18.1%
Terminal *(d)*	4/38 (11%)	6/35 (17%)	7/43 (16%)
Statistical Tests *(e)*			
Life Table	P=0.216	P=0.148	P=0.239
Incidental Tumor Test	P=0.199	P=0.210	P=0.212
Cochran-Armitage Trend Test	P=0.152		
Fisher Exact Test		P=0.178	P=0.178
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	31/49 (63%)	25/49 (51%)	34/49 (69%)
Adjusted *(c)*	70.4%	57.2%	72.3%
Terminal *(d)*	25/38 (66%)	17/35 (49%)	30/43 (70%)
Statistical Tests *(e)*			
Life Table	P=0.514N	P=0.301N	P=0.529N
Incidental Tumor Test	P=0.392	P=0.076N	P=0.349
Cochran-Armitage Trend Test	P=0.302		
Fisher Exact Test		P=0.154N	P=0.335

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Pituitary: Carcinoma			
Tumor Rates			
Overall *(b)*	0/49 (0%)	2/49 (4%)	3/49 (6%)
Adjusted *(c)*	0.0%	5.7%	7.0%
Terminal *(d)*	0/38 (0%)	2/35 (6%)	3/43 (7%)
Statistical Tests *(e)*			
Life Table	P=0.106	P=0.220	P=0.144
Incidental Tumor Test	P=0.106	P=0.220	P=0.144
Cochran-Armitage Trend Test	P=0.082		
Fisher Exact Test		P=0.247	P=0.121
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	31/49 (63%)	27/49 (55%)	37/49 (76%)
Adjusted *(c)*	70.4%	62.0%	78.7%
Terminal *(d)*	25/38 (66%)	19/35 (54%)	33/43 (77%)
Statistical Tests *(e)*			
Life Table	P=0.360	P=0.438N	P=0.408
Incidental Tumor Test	P=0.188	P=0.159N	P=0.145
Cochran-Armitage Trend Test	P=0.123		
Fisher Exact Test		P=0.269N	P=0.137
Thyroid: Follicular-Cell Adenoma			
Tumor Rates			
Overall *(b)*	0/47 (0%)	2/47 (4%)	17/48 (35%)
Adjusted *(c)*	0.0%	5.3%	37.7%
Terminal *(d)*	0/36 (0%)	1/35 (4%)	15/43 (35%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.226	P<0.001
Incidental Tumor Test	P<0.001	P=0.220	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.247	P<0.001
Thyroid: Follicular-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	0/47 (0%)	4/47 (9%)	19/48 (40%)
Adjusted *(c)*	0.0%	10.1%	42.1%
Terminal *(d)*	0/36 (0%)	2/35 (6%)	17/43 (40%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.062	P<0.001
Incidental Tumor Test	P<0.001	P=0.099	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.058	P<0.001
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	0/47 (0%)	3/47 (6%)	6/48 (13%)
Adjusted *(c)*	0.0%	8.6%	14.0%
Terminal *(d)*	0/36 (0%)	3/35 (9%)	6/43 (14%)
Statistical Tests *(e)*			
Life Table	P=0.020	P=0.116	P=0.029
Incidental Tumor Test	P=0.020	P=0.116	P=0.029
Cochran-Armitage Trend Test	P=0.011		
Fisher Exact Test		P=0.121	P=0.014

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	1/47 (2%)	5/47 (11%)	7/48 (15%)
Adjusted *(c)*	2.3%	14.3%	16.3%
Terminal *(d)*	0/36 (0%)	5/35 (14%)	7/43 (16%)
Statistical Tests *(e)*			
Life Table	P=0.048	P=0.096	P=0.054
Incidental Tumor Test	P=0.035	P=0.094	P=0.032
Cochran-Armitage Trend Test	P=0.027		
Fisher Exact Test		P=0.102	P=0.032
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(b)*	10/50 (20%)	14/50 (28%)	9/50 (18%)
Adjusted *(c)*	25.5%	34.7%	19.7%
Terminal *(d)*	9/38 (24%)	10/35 (29%)	7/43 (16%)
Statistical Tests *(e)*			
Life Table	P=0.345N	P=0.192	P=0.395N
Incidental Tumor Test	P=0.346N	P=0.319	P=0.405N
Cochran-Armitage Trend Test	P=0.452N		
Fisher Exact Test		P=0.241	P=0.500N
Mammary Gland: Adenocarcinoma			
Tumor Rates			
Overall *(b)*	4/50 (8%)	4/50 (8%)	0/50 (0%)
Adjusted *(c)*	9.3%	10.4%	0.0%
Terminal *(d)*	2/38 (5%)	3/35 (9%)	0/43 (0%)
Statistical Tests *(e)*			
Life Table	P=0.054N	P=0.610	P=0.058N
Incidental Tumor Test	P=0.090N	P=0.601	P=0.138N
Cochran-Armitage Trend Test	P=0.060N		
Fisher Exact Test		P=0.643	P=0.059N
Clitoral Gland: Adenoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	4/50 (8%)	5/50 (10%)
Adjusted *(c)*	5.3%	10.6%	11.3%
Terminal *(d)*	2/38 (5%)	3/35 (9%)	4/43 (9%)
Statistical Tests *(e)*			
Life Table	P=0.217	P=0.307	P=0.264
Incidental Tumor Test	P=0.213	P=0.415	P=0.228
Cochran-Armitage Trend Test	P=0.169		
Fisher Exact Test		P=0.339	P=0.218
Clitoral Gland: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	4/50 (8%)	5/50 (10%)
Adjusted *(c)*	7.9%	10.6%	11.3%
Terminal *(d)*	3/38 (8%)	3/35 (9%)	4/43 (9%)
Statistical Tests *(e)*			
Life Table	P=0.353	P=0.462	P=0.419
Incidental Tumor Test	P=0.353	P=0.575	P=0.378
Cochran-Armitage Trend Test	P=0.290		
Fisher Exact Test		P=0.500	P=0.357

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(b)*	11/48 (23%)	15/50 (30%)	12/50 (24%)
Adjusted *(c)*	26.4%	38.7%	27.9%
Terminal *(d)*	8/38 (21%)	12/35 (34%)	12/43 (28%)
Statistical Tests *(e)*			
Life Table	P=0.503N	P=0.194	P=0.564N
Incidental Tumor Test	P=0.468	P=0.219	P=0.484
Cochran-Armitage Trend Test	P=0.501		
Fisher Exact Test		P=0.286	P=0.545
Uterus: Endometrial Stromal Sarcoma			
Tumor Rates			
Overall *(b)*	3/48 (6%)	0/50 (0%)	1/50 (2%)
Adjusted *(c)*	6.8%	0.0%	2.1%
Terminal *(d)*	1/38 (3%)	0/35 (0%)	0/43 (0%)
Statistical Tests *(e)*			
Life Table	P=0.169N	P=0.134N	P=0.288N
Incidental Tumor Test	P=0.398N	P=0.204N	P=0.582N
Cochran-Armitage Trend Test	P=0.166N		
Fisher Exact Test		P=0.114N	P=0.293N
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(b)*	13/48 (27%)	15/50 (30%)	13/50 (26%)
Adjusted *(c)*	30.5%	38.7%	29.4%
Terminal *(d)*	9/38 (24%)	12/35 (34%)	12/43 (28%)
Statistical Tests *(e)*			
Life Table	P=0.412N	P=0.334	P=0.463N
Incidental Tumor Test	P=0.545	P=0.396	P=0.546
Cochran-Armitage Trend Test	P=0.495N		
Fisher Exact Test		P=0.462	P=0.542N
Ovary: Granulosa-Cell Tumor			
Tumor Rates			
Overall *(b)*	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted *(c)*	0.0%	8.6%	4.5%
Terminal *(d)*	0/38 (0%)	3/35 (9%)	1/43 (2%)
Statistical Tests *(e)*			
Life Table	P=0.237	P=0.107	P=0.256
Incidental Tumor Test	P=0.206	P=0.107	P=0.191
Cochran-Armitage Trend Test	P=0.202		
Fisher Exact Test		P=0.121	P=0.247
Ovary: Granulosa-Cell Tumor or Carcinoma			
Tumor Rates			
Overall *(b)*	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted *(c)*	0.0%	10.9%	4.5%
Terminal *(d)*	0/38 (0%)	3/35 (9%)	1/43 (2%)
Statistical Tests *(e)*			
Life Table	P=0.258	P=0.054	P=0.256
Incidental Tumor Test	P=0.199	P=0.064	P=0.191
Cochran-Armitage Trend Test	P=0.222		
Fisher Exact Test		P=0.059	P=0.247

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

(a) Dosed groups received doses of 150 or 300 ppm of 4,4'-methylenedianiline as the dihydrochloride in the drinking water.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)*

	Control	Low Dose	High Dose
Subcutaneous Tissue: Sarcoma			
Tumor Rates			
Overall *(b)*	4/49 (8%)	1/50 (2%)	2/50(4%)
Adjusted *(c)*	8.9%	2.6%	5.6%
Terminal *(d)*	1/40 (3%)	1/39 (3%)	0/32 (0%)
Statistical Tests *(e)*			
Life Table	P=0.307N	P=0.200N	P=0.424N
Incidental Tumor Test	P=0.149N	P=0.252N	P=0.184N
Cochran-Armitage Trend Test	P=0.231N		
Fisher Exact Test		P=0.175N	P=0.329N
Subcutaneous Tissue: Sarcoma or Neurofibrosarcoma			
Tumor Rates			
Overall *(b)*	4/49 (8%)	2/50 (4%)	2/50 (4%)
Adjusted *(c)*	8.9%	4.6%	5.6%
Terminal *(d)*	1/40(3%)	1/39 (3%)	0/32 (0%)
Statistical Tests *(e)*			
Life Table	P=0.325N	P=0.362N	P=0.424N
Incidental Tumor Test	P=0.117N	P=0.347N	P=0.184N
Cochran-Armitage Trend Test	P=0.244N		
Fisher Exact Test		P=0.329N	P=0.329N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	12/49 (24%)	9/49 (18%)	3/49 (6%)
Adjusted *(c)*	29.1%	21.3%	9.4%
Terminal *(d)*	11/40 (28%)	6/38 (16%)	3/32 (9%)
Statistical Tests *(e)*			
Life Table	P=0.031N	P=0.360N	P=0.035N
Incidental Tumor Test	P=0.017N	P=0.313N	P=0.030N
Cochran-Armitage Trend Test	P=0.010N		
Fisher Exact Test		P=0.312N	P=0.011N
Lung: Alveolar/Bronchiolar Carcinoma			
Tumor Rates			
Overall *(b)*	1/49 (2%)	4/49 (8%)	1/49 (2%)
Adjusted *(c)*	2.5%	10.5%	3.1%
Terminal *(d)*	1/40 (3%)	4/38 (11%)	1/32 (3%)
Statistical Tests *(e)*			
Life Table	P=0.513	P=0.164	P=0.711
Incidental Tumor Test	P=0.513	P=0.164	P=0.711
Cochran-Armitage Trend Test	P=0.601		
Fisher Exact Test		P=0.181	P=0.753
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	13/49 (27%)	12/49 (24%)	4/49 (8%)
Adjusted *(c)*	31.6%	28.7%	12.5%
Terminal *(d)*	12/40 (30%)	9/38 (24%)	4/32 (13%)
Statistical Tests *(e)*			
Life Table	P=0.049N	P=0.554N	P=0.048N
Incidental Tumor Test	P=0.029N	P=0.510N	P=0.041N
Cochran-Armitage Trend Test	P=0.015N		
Fisher Exact Test		P=0.500N	P=0.015N

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Hematopoietic System: All Malignant Lymphoma			
Tumor Rates			
Overall *(b)*	10/49 (20%)	9/50 (18%)	11/50 (22%)
Adjusted *(c)*	23.2%	22.5%	25.3%
Terminal *(d)*	8/40 (20%)	8/39 (21%)	3/32 (9%)
Statistical Tests *(e)*			
Life Table	P=0.291	P=0.524N	P=0.344
Incidental Tumor Test	P=0.502N	P=0.456N	P=0.424N
Cochran-Armitage Trend Test	P=0.470		
Fisher Exact Test		P=0.480N	P=0.521
Circulatory System: Hemangioma			
Tumor Rates			
Overall *(b)*	3/49 (6%)	6/50 (12%)	4/50 (8%)
Adjusted *(c)*	7.5%	15.0%	12.5%
Terminal *(d)*	3/40 (7%)	5/39 (13%)	4/32 (13%)
Statistical Tests *(e)*			
Life Table	P=0.301	P=0.233	P=0.379
Incidental Tumor Test	P=0.332	P=0.211	P=0.379
Cochran-Armitage Trend Test	P=0.442		
Fisher Exact Test		P=0.254	P=0.511
Circulatory System: Angiosarcoma or Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	5/49 (10%)	3/50 (6%)	7/50 (14%)
Adjusted *(c)*	11.7%	7.7%	19.8%
Terminal *(d)*	3/40 (7%)	3/39 (8%)	5/32 (16%)
Statistical Tests *(e)*			
Life Table	P=0.199	P=0.379N	P=0.248
Incidental Tumor Test	P=0.323	P=0.423N	P=0.423
Cochran-Armitage Trend Test	P=0.320		
Fisher Exact Test		P=0.346N	P=0.394
Circulatory System: Hemangioma, Hemangiosarcoma, or Angiosarcoma			
Tumor Rates			
Overall *(b)*	7/49 (14%)	9/50 (18%)	8/50 (16%)
Adjusted *(c)*	16.5%	22.5%	22.8%
Terminal *(d)*	5/40 (13%)	8/39 (21%)	6/32 (19%)
Statistical Tests *(e)*			
Life Table	P=0.276	P=0.371	P=0.331
Incidental Tumor Test	P=0.414	P=0.314	P=0.505
Cochran-Armitage Trend Test	P=0.463		
Fisher Exact Test		P=0.410	P=0.517
Liver: Hepatocellular Adenoma			
Tumor Rates			
Overall *(b)*	7/49 (14%)	10/50 (20%)	8/50 (16%)
Adjusted *(c)*	17.5%	24.7%	23.3%
Terminal *(d)*	7/40 (18%)	9/39 (23%)	6/32 (19%)
Statistical Tests *(e)*			
Life Table	P=0.268	P=0.275	P=0.323
Incidental Tumor Test	P=0.314	P=0.307	P=0.384
Cochran-Armitage Trend Test	P=0.464		
Fisher Exact Test		P=0.314	P=0.517

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma			
Tumor Rates			
Overall *(b)*	10/49 (20%)	33/50 (66%)	29/50 (58%)
Adjusted *(c)*	23.3%	70.2%	74.0%
Terminal *(d)*	8/40 (20%)	25/39 (64%)	22/32 (69%)
Statistical Tests *(e)*			
Life Table	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	17/49 (35%)	43/50 (86%)	37/50 (74%)
Adjusted *(c)*	40.1%	89.6%	90.2%
Terminal *(d)*	15/40 (38%)	34/39 (87%)	28/32 (88%)
Statistical Tests *(e)*			
Life Table	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Adrenal: Adenoma			
Tumor Rates			
Overall *(b)*	3/48 (6%)	1/49 (2%)	0/49 (0%)
Adjusted *(c)*	7.7%	2.6%	0.0%
Terminal *(d)*	3/39 (8%)	1/39 (3%)	0/32 (0%)
Statistical Tests *(e)*			
Life Table	P=0.078N	P=0.305N	P=0.158N
Incidental Tumor Test	P=0.078N	P=0.305N	P=0.158N
Cochran-Armitage Trend Test	P=0.058N		
Fisher Exact Test		P=0.301N	P=0.117N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	2/48 (4%)	12/49 (24%)	14/49 (29%)
Adjusted *(c)*	5.1%	29.8%	39.5%
Terminal *(d)*	2/39 (5%)	11/39 (28%)	11/32 (34%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.004	P<0.001
Incidental Tumor Test	P<0.001	P=0.006	P<0.001
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.004	P=0.001
Thyroid: Follicular-Cell Adenoma			
Tumor Rates			
Overall *(b)*	0/47 (0%)	3/49 (6%)	16/49 (33%)
Adjusted *(c)*	0.0%	7.0%	42.8%
Terminal *(d)*	0/39 (0%)	1/38 (3%)	11/32 (34%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.118	P<0.001
Incidental Tumor Test	P<0.001	P=0.146	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.129	P<0.001

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

(a) Dosed groups received doses of 150 or 300 ppm of 4,4'-methylenedianiline as the dihydrochloride in the drinking water.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)*

	Control	Low Dose	High Dose
Subcutaneous Tissue: Sarcoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted *(c)*	5.0%	7.2%	0.0%
Terminal *(d)*	2/40 (5%)	2/38 (5%)	0/37 (0%)
Statistical Tests *(e)*			
Life Table	P=0.221N	P=0.481	P=0.256N
Incidental Tumor Test	P=0.182N	P=0.481	P=0.256N
Cochran-Armitage Trend Test	P=0.202N		
Fisher Exact Test		P=0.500	P=0.247N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	2/50 (4%)	6/49 (12%)
Adjusted *(c)*	2.5%	5.3%	16.7%
Terminal *(d)*	1/40 (3%)	2/38 (5%)	6/36 (17%)
Statistical Tests *(e)*			
Life Table	P=0.021	P=0.482	P=0.042
Incidental Tumor Test	P=0.021	P=0.482	P=0.042
Cochran-Armitage Trend Test	P=0.027		
Fisher Exact Test		P=0.500	P=0.053
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	3/50 (6%)	8/49 (16%)
Adjusted *(c)*	5.0%	7.9%	21.4%
Terminal *(d)*	2/40 (5%)	3/38 (8%)	7/36 (19%)
Statistical Tests *(e)*			
Life Table	P=0.017	P=0.477	P=0.034
Incidental Tumor Test	P=0.017	P=0.477	P=0.032
Cochran-Armitage Trend Test	P=0.023		
Fisher Exact Test		P=0.500	P=0.043
Hematopoietic System: All Malignant Lymphoma			
Tumor Rates			
Overall *(b)*	13/50 (26%)	28/50 (56%)	29/50 (58%)
Adjusted *(c)*	31.7%	61.9%	64.3%
Terminal *(d)*	12/40 (30%)	21/38 (55%)	21/37 (57%)
Statistical Tests *(e)*			
Life Table	P=0.001	P=0.002	P=0.001
Incidental Tumor Test	P=0.001	P=0.002	P=0.001
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		P=0.002	P=0.001
Circulatory System: Hemangioma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted *(c)*	4.6%	2.6%	8.1%
Terminal *(d)*	1/40 (3%)	1/38 (3%)	3/37 (8%)
Statistical Tests *(e)*			
Life Table	P=0.375	P=0.509N	P=0.472
Incidental Tumor Test	P=0.365	P=0.575N	P=0.458
Cochran-Armitage Trend Test	P=0.399		
Fisher Exact Test		P=0.500N	P=0.500

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Circulatory System: Angiosarcoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted *(c)*	2.2%	2.6%	10.8%
Terminal *(d)*	0/40 (0%)	1/38 (3%)	4/37 (11%)
Statistical Tests *(e)*			
Life Table	P=0.090	P=0.759	P=0.162
Incidental Tumor Test	P=0.089	P=0.693	P=0.155
Cochran-Armitage Trend Test	P=0.101		
Fisher Exact Test		P=0.753	P=0.181
Circulatory System: Angiosarcoma or Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted *(c)*	2.2%	4.9%	10.8%
Terminal *(d)*	0/40 (0%)	1/38 (3%)	4/37 (11%)
Statistical Tests *(e)*			
Life Table	P=0.106	P=0.502	P=0.162
Incidental Tumor Test	P=0.119	P=0.592	P=0.155
Cochran-Armitage Trend Test	P=0.118		
Fisher Exact Test		P=0.500	P=0.181
Circulatory System: Hemangioma, Angiosarcoma, or Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	3/50 (6%)	6/50 (12%)
Adjusted *(c)*	6.7%	7.5%	16.2%
Terminal *(d)*	1/40 (3%)	2/38 (5%)	6/37 (16%)
Statistical Tests *(e)*			
Life Table	P=0.158	P=0.655	P=0.216
Incidental Tumor Test	P=0.167	P=0.663N	P=0.199
Cochran-Armitage Trend Test	P=0.178		
Fisher Exact Test		P=0.661	P=0.243
Liver: Hepatocellular Adenoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	9/50 (18%)	12/50 (24%)
Adjusted *(c)*	7.5%	23.7%	31.4%
Terminal *(d)*	3/40 (7%)	9/38 (24%)	11/37 (30%)
Statistical Tests *(e)*			
Life Table	P=0.006	P=0.049	P=0.008
Incidental Tumor Test	P=0.006	P=0.049	P=0.008
Cochran-Armitage Trend Test	P=0.010		
Fisher Exact Test		P=0.061	P=0.011
Liver: Hepatocellular Carcinoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	6/50 (12%)	11/50 (22%)
Adjusted *(c)*	2.5%	15.3%	28.8%
Terminal *(d)*	1/40 (3%)	5/38 (13%)	10/37 (27%)
Statistical Tests *(e)*			
Life Table	P=0.001	P=0.053	P=0.002
Incidental Tumor Test	P=0.001	P=0.080	P=0.002
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.056	P=0.002

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	4/50 (8%)	15/50 (30%)	23/50 (46%)
Adjusted *(c)*	10.0%	38.4%	58.8%
Terminal *(d)*	4/40 (10%)	14/38 (37%)	21/37 (57%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.003	P<0.001
Incidental Tumor Test	P<0.001	P=0.005	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.005	P<0.001
Stomach: Papillomatosis			
Tumor Rates			
Overall *(b)*	3/50 (6%)	1/49 (2%)	0/48 (0%)
Adjusted *(c)*	7.5%	2.7%	0.0%
Terminal *(d)*	3/40 (8%)	1/37 (3%)	0/36 (0%)
Statistical Tests *(e)*			
Life Table	P=0.072N	P=0.333N	P=0.140N
Incidental Tumor Test	P=0.072N	P=0.333N	P=0.140N
Cochran-Armitage Trend Test	P=0.064N		
Fisher Exact Test		P=0.316N	P=0.129N
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	12/42 (29%)	8/40 (20%)	14/39 (36%)
Adjusted *(c)*	34.3%	25.0%	45.7%
Terminal *(d)*	12/35 (34%)	8/32 (25%)	12/28 (43%)
Statistical Tests *(e)*			
Life Table	P=0.162	P=0.288N	P=0.185
Incidental Tumor Test	P=0.190	P=0.288N	P=0.233
Cochran-Armitage Trend Test	P=0.281		
Fisher Exact Test		P=0.260N	P=0.320
Thyroid: Follicular Cell Adenoma			
Tumor Rates			
Overall *(b)*	0/50 (0%)	1/47 (2%)	13/50 (26%)
Adjusted *(c)*	0.0%	2.7%	32.9%
Terminal *(d)*	0/40 (0%)	1/37 (3%)	11/37 (30%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.484	P<0.001
Incidental Tumor Test	P<0.001	P=0.484	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.485	P<0.001
Thyroid: Follicular Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	0/50 (0%)	1/47 (2%)	15/50 (30%)
Adjusted *(c)*	0.0%	2.7%	38.1%
Terminal *(d)*	0/40 (0%)	1/37 (3%)	13/37 (35%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.484	P<0.001
Incidental Tumor Test	P<0.001	P=0.484	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.485	P<0.001

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Ovary: Tubular Adenoma			
Tumor Rates			
Overall *(b)*	2/43 (5%)	3/38 (8%)	0/34 (0%)
Adjusted *(c)*	5.6%	10.3%	0.0%
Terminal *(d)*	2/36 (6%)	3/29 (10%)	0/27 (0%)
Statistical Tests *(e)*			
Life Table	P=0.287N	P=0.401	P=0.303N
Incidental Tumor Test	P=0.287N	P=0.401	P=0.303N
Cochran-Armitage Trend Test	P=0.267N		
Fisher Exact Test		P=0.441	P=0.309N

(a) Dosed groups received doses of 150 or 300 ppm of 4,4'-methylenedianiline as the dihydrochloride in the drinking water.

(b) Number of tumor bearing animals/number of animals examined at the site.

(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

(d) Observed tumor incidence at terminal kill.

(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

APPENDIX G

ANALYSIS OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE MIDWEST RESEARCH INSTITUTE

APPENDIX G

A. ELEMENTAL ANALYSIS

Element:	C	H	N	Cl
Theory	57.57	5.95	10.33	26.15
Lot No. A6A				
Determined	57.30	5.90	10.14	26.5±0.2(δ)
	57.33	5.94	10.10	
Lot No. A8				
Determined	55.58	6.01	9.93	26.31
	55.69	6.00	9.93	26.26

B. WATER ANALYSIS (Karl Fischer)

Lot No. A8 3.54% ± 0.34%

C. TITRATION (Nonaqueous titration of amine groups with perchloric acid)

Lot No. A6A 102% ± 1(δ)%

Lot No. A8 98.63% ± 0.43 (δ)%

D. THIN LAYER CHROMATOGRAPHY

Plates:	Silica gel 60-F 254
Ref. Standard:	4,4'-Methylenedianiline
Visualization:	Ultraviolet, 254 and 366 nm and 1% aqueous potassium ferricyanide: 2% aqueous ferric chloride in 0.2% HCl (1:1)
Amount Spotted:	100 and 300 μg
1. System 1:	Benzene:methanol (80:20)
Lot No. A6A	R_f: 0.43 R_{st}: 1.04
Lot No. A8	R_f: 0.72 (slight trace), 0.67 (trace), 0.61 (major), origin (trace) R_{st}: 1.2, 1.1, 1.0, origin
2. System 2:	Ethyl acetate: hexane (50:50
Lot No. A6A	R_f: 0.34 (major), origin (slight trace, 254 nm only) R_{st}: 1.00, origin
Lot No. A8	R_f: 0.49 (slight trace), 0.41 (trace), 0.34 (major), origin (trace) R_{st}: 1.5, 1.3, 1.1, origin

E. MELTING POINT

Determined	Literature Value
Lot No. A6A 140°C (discoloration), 250°C to 279°C (decomposition) (visual, capillary)	288°C (Beilstein, 1918)
Lot No. A8 277°C to 278°C dec. (compound changed white to purple ~200°C; after melting evolved gas) (visual capillary)	
192° to 221°C dec. (decomposition began at 160°C) DuPont 900 DTA	

APPENDIX G

F. VAPOR-PHASE CHROMATOGRAPHY

Lot No. A6A

Instrument: Tracor MT 220
Detector: Flame ionization
Inlet temperature: 200°C
Detector temperature: 270°C
Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m x 4 mm I.D., glass
Oven temperature program: 5 min at 100°C, then 100°C to 200°C at 10°/min
Results: Major peak and four impurities

Peak	Retention Time (min)	Retention Time (Relative to 4,4'-Methylenedianiline Dihydrochloride)	Area (Percent of Methylenedianiline Dihydrochloride)
1	4.3	0.23	0.04
2	17.5	0.93	0.02
3	18.8	1.00	100
4	20.2	1.08	0.1
5	21.2	1.13	0.3

Lot No. A8

Instrument: Varian 3740
Detector: Flame ionization
Inlet temperature: 230°C
Detector temperature: 310°C
Carrier gas: Nitrogen
Carrier flow rate: 70 cc/min

1. System 1

Column: 3% OV-17 on 80/100 Supelcoport 1.8 M x 4 mm I.D., glass
Oven temperature program: 100°C, 5 min; 100° to 200°C at 10°C/min

Sample injected: A solution (7 μl) of 1% methylenedianiline dihydrochloride in methanol was used for the analysis. A 0.5% solution was used to quantitate the major peak and check for detector overload.

Results: Major peak and two impurities which totaled 1.3% of the major peak area.

Peak	Retention Time (min)	Retention Time (Relative to 4,4'-Methylenedianiline Dihydrochloride)	Area (Percent of Methylenedianiline Dihydrochloride)
1	19.9	0.96	1.0
2	20.8	1.00	100
3	21.6	1.04	0.25

2. System 2

Column: 3% SP-2100 on 80/100 Supelcoport, 1.8 m x 4 mm I.D., glass Oven temperature program: 100°C, 5 min; 100° to 250°C at 10°C/min

Sample injected: A solution (7 μl) of 1% methylenedianiline dihydrochloride in methanol was used for the analysis. A 0.5% solution (7 μl) was used to quantitate the major peak and check for detector overload.

Results: Major peak and two impurities which total 1.5% of the major peak area.

Peak	Retention Time (min)	Retention Time (Relative to 4,4'-Methylenedianiline Dihydrochloride)	Area (Percent of Methylenedianiline Dihydrochloride)
1	3.1	0.05	0.38
2	16.5	0.96	1.1
3	17.1	1.00	100

G. SPECTRAL DATA

Lot No. A8

1. Infrared

Instrument: Beckman IR-12
Cell: 1% in KBr
Results: See Figure 6

Spectrum consistent with literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible

Instrument: Cary 118

λ max (nm)	$\varepsilon \times 10^{-3}$	λ max (nm)	$\varepsilon \times 10^{-3}$
269.6 (shoulder)	0.81 ± 0.01	245	2.08 (Sadtler Standard Spectra)
244.3	2.20 ± 0.06		

No absorbance between 350 and 800 nm (visible range) at a concentration of 0.1 mg/ml.

Solvent: Methanol

Solvent: Methanol

3. Nuclear Magnetic Resonance

Instrument: Varian EM-360A
Solvent: Deuterated water with internal sodium 3-trimethylsilylpropionate-2,2,3,3-d_4

Consistent with literature spectrum (Sadtler Standard Spectra)

Assignments: See Figure 7
(a) s, δ 3.90 ppm
(b) s, δ 7.18 to 7.60 ppm
(c) s, δ 5.18 ppm (HDO from -NH_2, HCl)

Integration Ratios:
(a) 2.04
(b) 7.95
(c) -

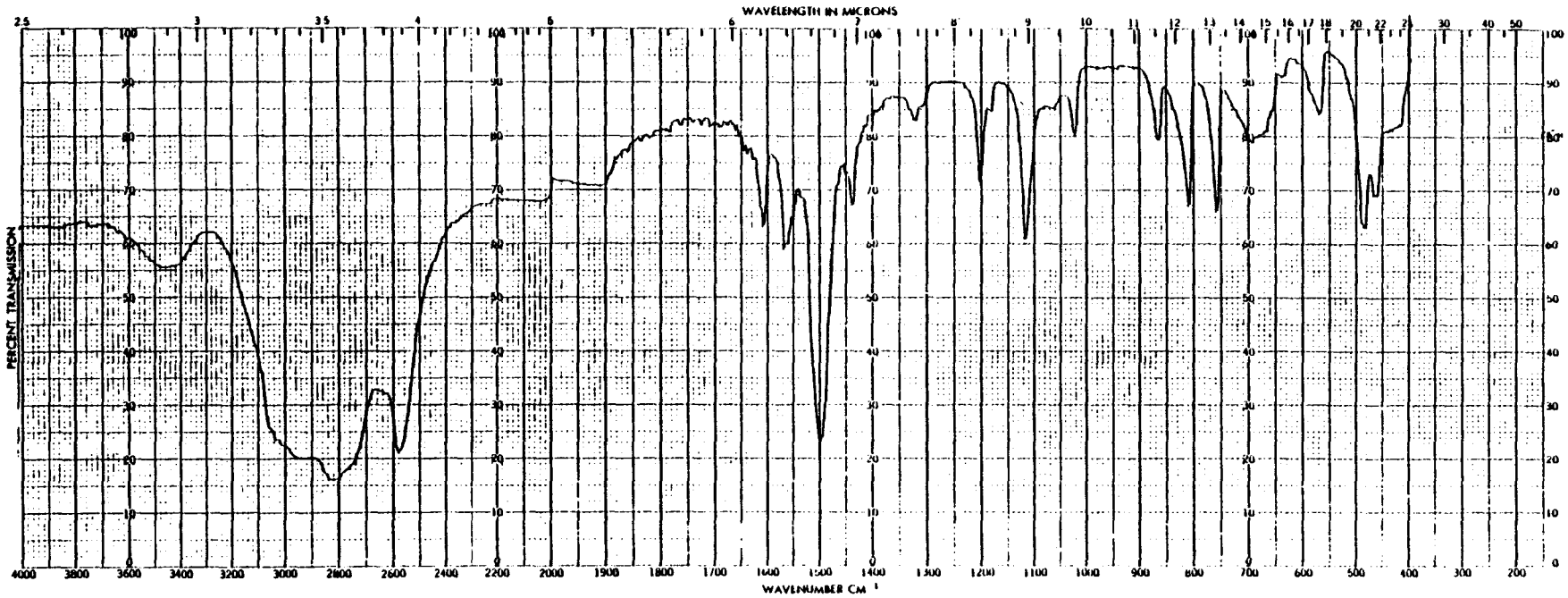


Figure 6. Infrared Absorption Spectrum of 4,4'-Methylenedianiline Dihydrochloride (Lot No. A8)

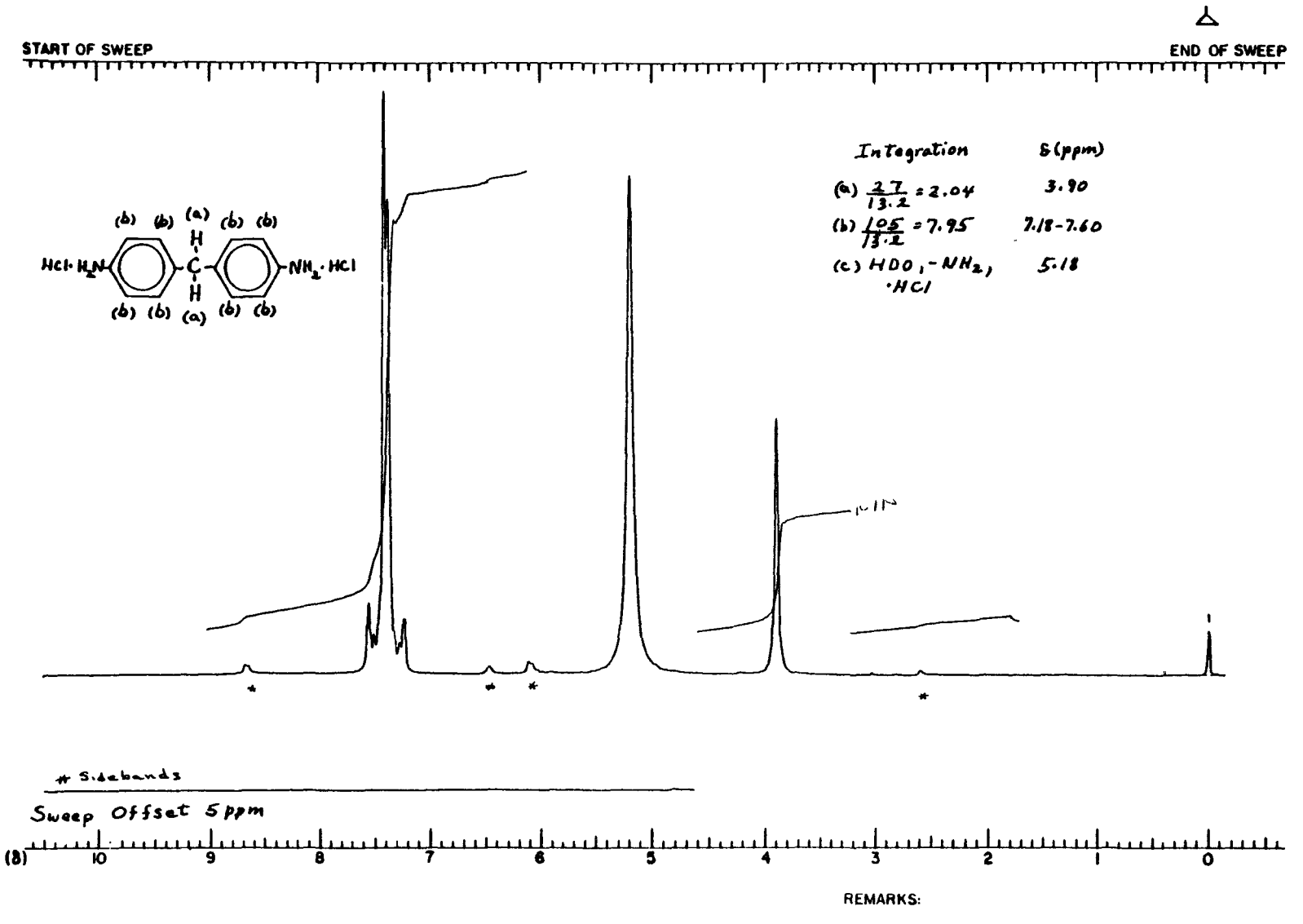


Figure 7. Nuclear Magnetic Resonance Spectrum of 4,4'-Methylenedianiline Dihydrochloride (Lot No. A8)

APPENDIX H

ANALYSIS OF AQUEOUS SOLUTIONS OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE FOR STABILITY OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

APPENDIX H

A. SAMPLE PREPARATION AND STORAGE

4,4'-Methylenedianiline dihydrochloride (9.9615 ± 0.0001 g) was dissolved in 1 liter of distilled water (a 0.9961% ± 0.0003% solution). A 100-ml portion of this solution was further diluted to 1 liter to provide a 0.09961% ± 0.00004% solution. These two solutions correspond to concentrations of 9,961 and 996.1 ppm of the dihydrochloride salt or 7,283 and 728.3 ppm, respectively, of the free 4,4'-methylenedianiline base.

Each of the above solutions was equally distributed between three 600-ml animal-cage water bottles fitted with black rubber stoppers and sipper tubes. The solutions were kept in these bottles throughout the stability testing period, unprotected from light. Aliquots (2 ml) were withdrawn through the tubes for zero-time analysis and after 1, 3, and 7 days.

B. EXTRACTION AND ANALYSIS

To each 2-ml stability sample or blank in an 8.5-ml septum vial was added 1 ml of 10% aqueous sodium hydroxide (this results in 3 ml of a solution which is 0.83 M in sodium hydroxide, having a calculated pH ≈ 13.9) and 3 ml of benzene. This two-phase mixture was then sealed in the vial and thoroughly shaken, both by hand and on a vortex mixer. After the two phases had separated, samples of the upper (benzene) layer in the vial were removed by microsyringe and injected (in triplicate) directly into a gas chromatograph for analysis. The chromatographic system is described below.

Instrument: Varian 2400
Column: 3% OV-225 on 80/100 mesh Supelcoport, 1.8 m x 2 mm I.D., glass
Detection: Flame ionization
Temperatures: Inlet, 290°C; oven, 250°C; isothermal detector, 300°C
Carrier gas: Nitrogen; flow rate, 40 cc/min
Retention time of nominal compound: 4.0 min
Reference standard: 4,4'-Methylenedianiline free base (correction made for molecular weight difference from the 2HCl salt)

C. RESULTS

The error figures in this and the following table are standard deviations of the nine analytical values obtained (triplicate gc injections of three separate solutions at each concentration level) at each storage interval, propagated by standard numerical methods in the correction for spike recovery yield.

1. 1.0% Concentration

Storage Time (Days)	Average Percent Chemical Found in Chemical/ Vehicle Mixture *(a)*
1	1.08 ± 0.09
3	0.98 ± 0.09
7	0.98 ± 0.09

(a) Corrected for a spike recovery yield of 77% ± 5%; concentration of original dose solutions, 0.9961% ± 0.0003%.

2. 0.1% Concentration

Storage Time (Days)	Average Percent Chemical Found in Chemical/ Vehicle Mixture *(a)*
1	0.098 ± 0.005
3	0.102 ± 0.005
7	0.098 ± 0.009

(a) Corrected for a spike recovery yield of 77% ± 5%; concentration of original dose solutions, 0.09961% ± 0.0004%.

D. CONCLUSION

4,4'-Methylenedianiline dihydrochloride is analytically stable in water solution at room temperature, in concentrations of 1.0% and 0.1%. The 1.0% solutions began to acquire a light brown coloration after 1 hour (which gradually darkened over the testing period), although they remained free from any turbidity. The 0.1% solutions remained both clear and colorless over the entire period. These solutions were not protected from light. Thus, there was a visually detectable change in the 1.0% solutions which was not detected by the gas chromatographic analytical method, whereas no such change was apparent with the 0.1% solutions. The observed color change may indicate light catalyzed oxidation of the 4,4'-methylenedianiline in the more concentrated solution, but this has not been confirmed experimentally.

APPENDIX I

ANALYSIS OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE IN WATER FOR CONCENTRATION OF 4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE

TABLE I1. ANALYSIS OF FORMULATED DRINKING WATER *(a)*

Date Mixed	Date Used (week of)	Concentration of 4,4'-Methylenedianiline Dihydrochloride in Water *(b)*	
		150 ppm	300 ppm
09/13/78	09/14/78		275
11/14/78	11/15/78	155	290
01/17/79	01/18/79	155	275
03/21/79	03/22/79	156	276 (324, c)
04/04/79	04/05/79	153	290
06/13/79	06/14/79	150	300
07/25/79	07/26/79	150	300
10/17/79	10/18/79	148	290
12/05/79	12/06/79	149	290
12/26/79	12/27/79	148	287
01/30/80	01/31/80	153 (148, c)	306
04/23/80	04/24/80	150	295
06/25/80	06/26/80	150	300
08/13/80	08/14/80	160	290 (296, c)
	Mean (ppm)	152.1	290.3
	Standard deviation	3.62	9.75
	Coefficient of variation (%)	2.4	3.4
	Range (ppm)	148-160	275-306
	Number of samples	13	14

(a) The sample in tap water was diluted with 95% ethanol (0.1 ml to 10 ml) and the absorbance was measured at 241 nm in a Beckman DU spectrophotometer. The reference standard was prepared and diluted and read by the same procedure.

(b) The data presented are the average of the results of duplicate analyses.

(c) Reference analysis performed by Midwest Research Institute on a separate sample from the same batch.

* U.S. GOVERNMENT PRINTING OFFICE: 1983-381-132:3134