NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 233

CARCINOGENESIS BIOASSAY OF 2-BIPHENYLAMINE HYDROCHLORIDE

(CAS NO. 2185-92-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDY)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT
ON THE

CARCINOGENESIS BIOASSAY OF 2-BIPHENYLAMINE HYDROCHLORIDE

(CAS NO. 2185-92-4)

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

NATIONAL TOXICOLOGY PROGRAM
Box 12233
Research Triangle Park
North Carolina 27709
and
Bethesda, Maryland 20205

October 1982

NTP-81-35
NIH Publication No. 83-1789

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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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 is a potential hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

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

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

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650).

Single copies of this carcinogenesis bioassay technical report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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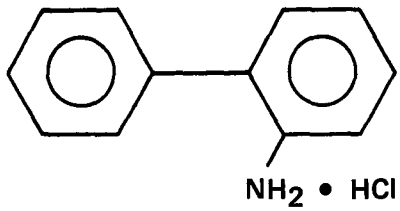

2-BIPHENYLAMINE HYDROCHLORIDE

CAS NO. 2185-92-4
$C_{12}H_{12}ClN$ Mol. Wt. 205.68

Single-dose, 14-day, and 13-week studies were conducted using technical-grade 2-biphenylamine (2-aminobiphenyl) containing up to 2.5% of the carcinogenic contaminant, 4-biphenylamine. When the contamination was recognized, analytical development was begun to purify the material. The salt, 2-biphenylamine hydrochloride, was prepared to obtain a more pure test product, which contained 0.006%-0.049% 4-biphenylamine. The prechronic tests were completed by the time purification was accomplished, so data from a second 14-day study with 2-biphenylamine hydrochloride were used to help set dose levels for the chronic study.

The results of the comparative 14-day studies showed that technical-grade 2-biphenylamine was more toxic to mice and rats than 2-biphenylamine hydrochloride as evidenced by greater incidence of splenomegaly and greater weight gain depression.

The technical-grade 2-biphenylamine caused a dose-related decrease in hemoglobin concentration and a dose-related increase in leucocyte count in male and female mice in the 13-week study. Hemosiderosis, congestion, and extramedullary hematopoeisis were present in the spleens of nearly all rats receiving 3,000 ppm or more of the chemical, and in nearly all mice with 1,000 ppm or more 2-biphenylamine in their diets.

The chronic study was conducted with the purified 2-biphenylamine hydrochloride by feeding diets containing 1,000 or 3,000 ppm 2-biphenylamine hydrochloride to groups of 49 or 50 F344/N rats and 50 B6C3F1 mice of each sex for 103 weeks. Groups of 50 rats and 50 mice of each sex served as controls. Survival of dosed male and female rats and dosed female mice was comparable with that of the corresponding controls. Survival of high-dose male mice was significantly ($P < 0.010$) less than that of low-dose and control male mice.

There were little or no differences in body weight changes for rats or mice between dosed and control groups, although there was a slight decrease in body weight gain at the end of the study for high-dose male (-11%) and female (-8%) rats.

Inflammatory cells and interstitial fibrosis were found in increased incidence in the kidneys of dosed male rats as compared with controls and were considered to be compound related. In addition to the increase in renal inflammation and fibrosis, dosed male rats had more focal cellular changes of the liver than did the controls. There were no increased or decreased incidences of tumors in rats that could be associated with chemical administration.

Myelomonocytic leukemia in male rats (control, 14/50; low-dose, 1/50; high-dose, 4/50) and fibroadenomas of the mammary gland in female rats (22/50, 10/49, 9/50) occurred with significantly ($P < 0.03$) decreasing trends and the incidences in the dosed groups were significantly ($P < 0.02$) lower than that in the controls.

Hemangiosarcomas from all sites occurred in female mice with a statistically significant ($P \leq 0.002$) positive trend. The observed incidence of hemangiosarcomas was 0/49, 1/50, and 7/50 in the control, low-dose, and high-dose groups, respectively. The incidence in the high-dose group was significantly

($P < 0.01$) higher than that in controls. The conclusion that this was due to 2-biphenylamine rather than the contaminant, 4-biphenylamine, is supported by the absence of urinary bladder tumors, which are common to 4-biphenylamine.

Hemangiosarcomas also occurred in male mice with a statistically significant positive trend ($P=0.040$ by a life table test), with incidences of 0/50, 2/50, and 3/50. None of the pairwise comparisons were statistically different. The development of hemangiosarcomas may have been curtailed in the high-dose group of male mice, since only 21/50 survived until the termination of the study. The hemangiosarcomas found in female mice are uncommon with only 6/816 (0.7%) previously seen in controls at the same laboratory. The rate for control male mice is equally low: 7/803 (0.9%).

Alveolar/bronchiolar adenomas of the lung occurred at a significantly ($P < 0.01$) decreased rate in male mice with an incidence in dose groups lower ($P < 0.05$) than that in controls.

Under the conditions of this bioassay, 2-biphenylamine hydrochloride was not carcinogenic for F344/N rats of either sex. 2-Biphenylamine hydrochloride was carcinogenic for B6C3F1 female mice, inducing hemangiosarcomas at various sites. The evidence for an association between the administration of 2-biphenylamine hydrochloride and the increased incidence of hemangiosarcomas in male mice was equivocal.

CONTRIBUTORS

The bioassay of 2-biphenylamine hydrochloride was conducted at EG&G Mason Research Institute, under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The chronic study was begun in February 1978 and completed in March 1980.

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The pathology report and selected slides were evaluated in February 1981 by the NTP Pathology Working Group, which included Drs. G. Reznik, G. Boorman, B. Gupta, and J. Ward from NTP; and Dr. P. Hildebrandt from Tracor Jitco.

The chemicals used in this bioassay of 2-biphenylamine hydrochloride were analyzed by the Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri 64110; analysis of the formulated diets and reanalysis of the bulk chemical was done by Mason Research Institute.

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SUMMARY OF PEER REVIEW COMMENTS ON THE BIOASSAY OF 2-BIPHENYLAMINE HYDROCHLORIDE

On June 23, 1981, this carcinogenesis bioassay report on 2-biphenylamine hydrochloride underwent peer review and was approved by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts at an open meeting held in Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. Breslow, as a principal reviewer for the report on the bioassay of 2-biphenylamine hydrochloride, agreed with the conclusion that, under the conditions of the bioassay, "purified" 2-biphenylamine hydrochloride was carcinogenic for female B6C3F1 mice, including hemangiosarcomas at various sites. Poor survival may have contributed to the incomplete statistical evidence for similar chemically-induced hemangiosarcoma development in male mice. 2-Biphenylamine hydrochloride was not carcinogenic for F344/N rats of either sex. He proposed additions relating primarily to negative trends. Control female rats had a higher incidence of myelomonocytic leukemia in comparison with dosed rats of like sex. However, the rates in dosed animals were within the range observed in past control series. A statistically significant negative trend in the incidence of lung adenomas was observed in male mice.

Dr. Breslow said the results of the life table trend test ($P < 0.001$) should be added to the evidence used in the abstract to claim an increase in incidence of hemangiosarcoma in female mice. He felt a major issue had to do with contamination of the test material with the 4-biphenylamine and with ruling out the possibility that the tumors were produced by the contaminants. Although hemangiosarcomas have not been reported for 4-biphenylamine, it would be useful to note specifically whether 4-biphenylamine has been tested in B6C3F1 mice. [A literature search was done on TOXLINE in September 1982, and no references were found linking 4-biphenylamine with tests in B6C3F1 mice.] Highlights not in the abstract which should be added include the fact that hemangiosarcomas produced in female animals are quite rare with only 6 out of 816 previously seen in control animals at the same laboratory and no more than 3 in any group of 50. Also, in addition to the increase in renal inflammation and fibrosis, dosed male rats had more focal cellular changes of the liver than did controls.

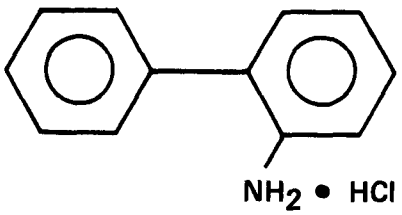
As a second principal reviewer, Dr. Williams concurred with Dr. Breslow's comments and added that the discussion relating to the way 2-biphenylamine produces hemangiosarcomas should be expanded. In other words, 2-biphenylamine, like many other aromatic amines, produces extramedullary hematopoiesis and hemosiderosis, probably as a result of producing methemoglobinemia. Production of methemoglobinemia has been associated with splenic hemangiosarcomas. Aniline is a classic example, producing hemangiosarcomas probably as a result of this perturbation of the hematopoietic system. He said the reference to the testing of 2-acetylaminobiphenyl by Miller *et al.* should be noted (Cancer Research *16*:525-534; 1956). 2-Acetylaminobiphenyl was found to be noncarcinogenic.

Dr. Swenberg said he thought metabolism studies had been done with reagent grade 2-biphenylamine, and, if so, these studies should be mentioned in the report. [Gorrod and Carey, Biochem. J. *119*; 52P-53P; 1970.] He commented on Dr. Williams' statement about aniline and announced that the Chemical Industry Institute of Toxicology was just completing a study on aniline in which fibrosarcomas were found to be the predominant tumor and hemangiosarcomas were minor tumors. Unlike results with 2-biphenylamine, these tumors were localized to the spleen.

Dr. Breslow moved that the report on the bioassay of 2-biphenylamine be accepted. Dr. Williams seconded the motion and the report was approved unanimously by the peer review panel.

I. INTRODUCTION

I. INTRODUCTION



2-BIPHENYLAMINE HYDROCHLORIDE

Molecular Weight: 205.7; Formula: $C_{12}H_{12}ClN$: (CAS No. 2185-92-4)

2-Biphenylamine (2-aminobiphenyl; CAS No. 90-41-5) is a chemical intermediate used in the manufacture of C.I. Acid Red 15 (Society of Dyers and Colourists, 1971). It is present as a contaminant in 4-biphenylamine (a rubber antioxidant) and in diphenylamine (a dye intermediate, stabilizer for nitrocellulose explosives, and a topical agent for prevention of screwworm infestation in animals), (IARC, 1972; Merck Index, 1968; Safe *et al.*, 1977). Technical-grade 2-biphenylamine contains 4-biphenylamine. This contaminant is a known urinary bladder carcinogen in humans (Melick *et al.*, 1955; Althouse *et al.*, 1980) and in animals (IARC, 1972). Production figures for 2-biphenylamine are not available (USITC, 1979).

Purified 2-biphenylamine has an oral LD_{50} value of 2.34 g/kg in Sprague-Dawley rats (Deichmann *et al.*, 1947).

Comparative short-term studies have demonstrated that 4-biphenylamine is more mutagenic than technical-grade 2-biphenylamine. 4-Biphenylamine was mutagenic after metabolic activation in a recombinant assay with *Saccharomyces cerevisiae* D3 (Simmon, 1979a) and for *Salmonella typhimurium* TA 98, TA 1537, TA 1538, and TA 100 (Anderson and Styles, 1978; Donahue *et al.*; 1978; Simmon, 1979b). Technical-grade 2-biphenylamine was mutagenic only for TA 100 at less than 4% of the reversion rate for 4-biphenylamine (Donahue *et al.*, 1978; Simmon, 1979b). 4-Biphenylamine elicited unscheduled DNA synthesis and induced transformation of rat embryo cells infected with Rauscher leukemia virus; technical-grade 2-biphenylamine was inactive in both tests (Freeman *et al.*, 1973; Williams, 1978). The diluted 24-hour urine of male Wistar rats administered 0.25 mg/kg 4-biphenylamine by intraperitoneal injection was mutagenic, with or without metabolic activation, for *Salmonella typhimurium* TA 1538; similar tests with technical-grade 2-biphenylamine were negative (Bos *et al.*, 1980). This suggests that metabolites of technical-grade 2-biphenylamine which may have appeared in the urine are not mutagenic, or were present in insufficient concentrations to produce mutations in the bacterial assay.

2-Biphenylamine was mutagenic in *Salmonella typhimurium* tester strains TA 98 and 100 (with metabolic activation); strains TA 1535 and 1537 were negative (NTP unpublished results). The 2-derivative has been selected for further testing in *Drosophila melanogaster*. 4-Biphenylamine was mutagenic in *Salmonella typhimurium* TA 98, 100, 1535, and 1537 (with activation) (NTP, 1980); this 4-derivative was negative in *Drosophila melanogaster* (sex-linked recessive lethal test) (NTP unpublished results). Test conditions for the Salmonella protocol include male Sprague-Dawley rat and Syrian hamster liver activation (Aroclor-1254) and preincubation suspension.

To study the metabolism of 2-biphenylamine in adult male albino rats, Gorrod and Carey (1970) administered by intraperitoneal injection 50 mg daily for 100 days (until the rats received a total of 5 g). From urine, "a small amount of unchanged 2-aminobiphenyl" was found; the isolated metabolites (and amount recovered) were: 2-amino-3-biphenylyl sulfate (300 mg), 2-amino-5-biphenylyl sulfate (1600 mg), and 2-amino-5-biphenylyl glucosiduronate (75 mg).

No 2-hydroxy- or 2-nitroso-metabolites were detected; similarly, methemoglobinemia was not observed. This indicates that these rats were not able to N-hydroxylate 2-aminobiphenyl, whereas 4-aminobiphenyl is metabolized in the rat by hydroxylation. Further, no metabolites conjugated at the amino group were found. The lack of a carcinogenic response in the F344/N rat (this study) may be due to its inability to form the N-hydroxy derivative of 2-aminobiphenyl.

A urinary metabolite of 4-biphenylamine in albino rats (N-hydroxy-4-acetylaminobiphenyl) produced tumors of the mammary gland in 10/10 female rats receiving 1.62 mMoles/kg in feed for 10 months (Miller *et al.*, 1961). A possible urinary metabolite of technical-grade 2-biphenylamine (2-acetylaminobiphenyl), was administered in the feed at 1.62 mMoles/kg, and did not produce mammary tumors in female rats (Miller *et al.*, 1956).

Workers exposed to 4-biphenylamine showed an increased incidence of bladder carcinomas. Animal studies revealed that oral administration of 4-biphenylamine produced bladder and liver cancer in mice and bladder papillomas and carcinomas in rabbits and dogs. Daily subcutaneous administration to rats of 4-biphenylamine in arachis oil increased the incidence of mammary gland and intestinal tumors (Althouse *et al.*, 1980; IARC, 1972).

The Bioassay Program tested 2-biphenylamine hydrochloride because of its structural relationship to and its possible use as a substitute for 4-biphenylamine, and because the 2-derivative had not been previously tested for carcinogenicity. Since the hydrochloride salt of 2-biphenylamine (CAS No. 2185-92-4) could be purified more easily than the free amine, this salt was chosen for use in the chronic bioassay.

II. METHODS AND MATERIALS

CHEMICAL ANALYSIS

PRECHRONIC STUDIES

Single-Dose Study with Technical-Grade 2-Biphenylamine

Fourteen-Day Study with Technical-Grade 2-Biphenylamine

Fourteen-Day Study with 2-Biphenylamine Hydrochloride

Thirteen-Week Study with Technical-Grade 2-Biphenylamine

Statistical Analyses of Hematology Data

CHRONIC STUDY

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Source and Specifications of Test Animals

Animal Maintenance

Preparation of Test Diets

Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSIS

Three lots of technical-grade 2-biphenylamine (Lot No. 081547, Lot No. CP 121175, and Lot No. 375) were obtained from Aldrich Chemical Co. (Milwaukee, WI), Chemical Procurement Co. (College Point, NY), and Mackenzie Chemical Co. (Central Islip, NY), respectively. When quantitated against a 4-biphenylamine standard, all three lots were found to contain 4-biphenylamine ranging in concentration from 1.2% for Lot No. CP 121175 to 2.5% for Lot 375.

The elemental analysis for Lot No. 081547 agreed with theoretical values, and vapor-phase chromatographic analysis indicated a purity of 98%. The infrared and nuclear magnetic resonance spectra were consistent with the structure and agreed with those reported in the literature (Appendix E). Lot No. 081547 was not purified but was used in the single-dose toxicity studies and in the first 14-day study.

For Lot No. CP 121175, the elemental analysis agreed with theoretical values; nonaqueous titration of the amine group with perchloric acid indicated a purity of 97.1%. Vapor-phase chromatographic analysis of this lot indicated a purity of greater than 98%. The infrared and nuclear magnetic resonance spectra were consistent with the structure and agreed with those reported in the literature (Appendix F).

A portion of Lot No. CP 121175 was used by Midwest Research Institute to prepare 2-biphenylamine hydrochloride. The preparation, designated Lot No. MRI 9-9-75 and found to contain 0.198% ± 0.071% 4-biphenylamine (Appendix G), was subsequently used in the second 14-day study.

Lot No. 375, which contained 2.5% 4-biphenylamine, was recrystallized by HET Chemical Co. (Central Islip, NY) from 95% methanol. This recrystallized product was converted to the 2-biphenylamine hydrochloride at Midwest Research Institute by first dissolving it in absolute ether, followed by the addition of concentrated hydrochloric acid to the solution. The 2-biphenylamine hydrochloride was further purified in four batches by reprecipitation from methanol (Appendix H). Each batch was then analyzed for 4-biphenylamine. (Methods and results are presented in Appendix H.) These batches contained from 0.006% to 0.049% 4-biphenylamine. These four batches (designated WN-1-61-RC1, WN-1-61-R2, WN-1-61-R3, and WN-1-61-R4) were used consecutively in the chronic studies. The preparation of the hydrochloride salt provided the best available method for reducing the level of 4-biphenylamine impurity and minimizing its possible confounding effect in the carcinogenesis bioassay of 2-biphenylamine.

Stability of technical-grade 2-biphenylamine at 100,000 ppm and of 2-biphenylamine hydrochloride at 5,000 and 10,000 ppm in formulated feed at -20°, 5°, 25°, and 45°C was determined at Midwest Research Institute by gas chromatography. The results indicated that technical-grade amine was stable for 2 weeks when mixed in feed and stored at a temperature as high as 45°C. However, 2-biphenylamine hydrochloride mixed in feed was found to be stable for only 1 week when stored at 25°C (Appendixes I and J).

PRECHRONIC STUDIES

Single-Dose Study with Technical-Grade 2-Biphenylamine

Male and female F344/N rats and B6C3F1 mice were obtained from Frederick Cancer Research Center (Frederick, MD) and observed for 1 week prior to the start of testing. Animals were 6-7 weeks old when the test began. Groups of two males and two females of each species were given single doses (0.001, 0.01, 0.1, 1.0, or 10.0 g/kg body weight) of technical-grade 2-biphenylamine (Lot No. 08157) in corn oil by gavage. Feed and water were available *ad libitum* after administration of the test material. Remaining details of animal maintenance are shown in Table 1.

Experimental animals were observed for 14 days for mortality and signs of toxicity. Animal weights were obtained at days 1, 7, and 14. Surviving animals were killed on day 14. Necropsies were performed on all animals. Any unusual observations were recorded.

Fourteen-Day Study with Technical-Grade 2-Biphenylamine

Male and female F344/N rats and B6C3F1 mice were obtained from Frederick Cancer Research Center (Frederick, MD). The animals were observed for 2 weeks before being placed on experimental diets. The animals were 6-7 weeks old at the start of the study.

Animals of the same sex and same species were housed in groups of five per cage. Animals were distributed among cages so that the average weight per cage was approximately equal for all animals of the same sex and species. Animals were fed *ad libitum* diets containing 0, 1,000, 3,000, 10,000, or 30,000 ppm technical-grade 2-biphenylamine for 14 days. Observations were made daily for mortality or signs of toxicity. Weights were obtained on days 1, 7, and 14, and surviving animals were killed on day 15. Gross necropsies were performed on all animals. Additional details of the experimental design are presented in Table 1.

Fourteen-Day Study with 2-Biphenylamine Hydrochloride

An unacceptable level (2.5%) of the known carcinogen, 4-biphenylamine, was found in the technical-grade 2-biphenylamine used in the initial 14-day study. A second 14-day study was conducted with 2-biphenylamine hydrochloride, containing 0.198% ± 0.017% of the impurity. The design of this study is similar to that described for the 14-day study with technical-grade 2-biphenylamine. The 2-biphenylamine hydrochloride salt was fed in the diet at levels of 0, 400, 1,200, 3,600, 12,100, or 36,300 ppm (Table 1).

Thirteen-Week Study with Technical-Grade 2-Biphenylamine

The 13-week study also utilized technical-grade 2-biphenylamine in the feed and was completed prior to the availability of the more pure hydrochloride salt. Even though the chemical lot contained 2.5% 4-biphenylamine as an impurity, the results were utilized to help set dose levels for a subsequent chronic study employing 2-biphenylamine hydrochloride.

Four-week-old male and female F344/N rats and B6C3F1 mice were obtained from Frederick Cancer Research Center (Frederick, MD) and were observed for 1 week prior to distribution and placement on experimental diets.

Animals of the same sex and species were housed in groups of five per cage. Animals were distributed among cages so that the average weight per cage was approximately equal for all animals of the same sex and species.

The technical-grade 2-biphenylamine was administered *ad libitum* in the feed at 0, 300, 1,000, 3,000, 10,000, and 30,000 ppm for 13 weeks. There were 10 males and 10 females of each species (Table 1).

Animals were observed twice daily for mortality and morbidity. Weekly clinical examinations were conducted on each animal. Body weight and feed consumption were recorded weekly.

At the completion of 1, 4, and 13 weeks of chemical administration, all animals were bled from the orbital sinuses with non-heparinized 20 µl micropipettes. The contents were diluted with labeled sample vials containing 10 ml ISOTON and mixed thoroughly. A 0.2-ml sample of this dilution was added to an additional 20 ml of ISOTON and mixed. The original 10-ml dilution was used for white cell count and hemoglobin determination after addition of 3 drops of lysing reagent. The 20-ml dilution was used for determination of red blood cell count and hematocrit. All determinations were made using a Coulter Counter ®, Model Fn.

At the time of orbital bleeding, tail blood samples were collected and used for preparation of blood smears. The smears were air dried, stained according to Wright's staining method, and used for differential leucocyte counts.

Surviving animals were killed with carbon dioxide at the end of the 13-week experimental period and necropsied. Animals that died earlier received a complete gross necrospy unless autolysis or cannibalism precluded all or part of the examination. The following tissues were examined: skin, mandibular lymph node, mammary gland, salivary gland, thigh muscle, sciatic nerve, sternebrae including marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroids, parathyroid, lymph nodes, esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, rectum, mesenteric lymph node, liver, pancreas, spleen, kidneys, adrenal, urinary bladder, seminal vesicles, prostate, testes, ovaries, uterus, brain, pituitary, spinal cord, and eyes.

All tissues were fixed for a minimum of 48 hours in 10% neutral buffered formalin, embedded in parablast, sectioned, and stained with hematoxylin and eosin. Selected kidneys

were cut in 4 μ sections and stained with Von-Kossa, Mallory trichrome, MacManus-PAS, or Prussian blue solutions.

Statistical Analyses of Hematology Data

For the hematology data, Jonckeere's test (Hollander and Wolfe, 1973) was employed to assess the significance of dose response trends. When a significant trend was detected, pairwise comparisons between dosed and control animals were made by the Mann-Whitney U-test (Hollander and Wolfe, 1973).

CHRONIC STUDY

Study Design

Diets containing 0, 1,000, or 3,000 ppm 2-biphenylamine hydrochloride (containing 0.006-0.049% 4-biphenylamine) were offered *ad libitum* to groups of rats and mice for 103 weeks. Initially there were 50 animals of each sex and species per group. A male was initially missexed and subsequently discarded from among the female rats, reducing the sample size to 49 (Table 1).

Source and Specifications of Test Animals

Four-week old male and female F344/N rats and B6C3F1 mice were obtained from Harlan Industries (Indianapolis, IN) and observed for 2 weeks. At 6-7 weeks of age animals were assigned five to a cage by sex and species, and cages were assigned to diets according to a table of random numbers.

Animal Maintenance

Rats and mice were housed in polycarbonate cages (Lab. Products Inc., Garfield, NJ) and covered with nonwoven polyester filter sheets. Cages and bedding were replaced twice weekly. Tap water was offered via the Edstrom Automatic Watering System (Edstrom Industries, Waterfield, WI). Animal room temperatures ranged from 17.2°C to 32.2°C. Room humidity was uncontrolled. Fluorescent light was provided for 12 hours per day. No other chemicals were on test in the same room.

Preparation of Test Diets

Diets containing 0, 1,000, or 3,000 ppm 2-biphenylamine hydrochloride were used in this study. Fresh diets were prepared every 7 days. Midwest Research Institute determined that 2-biphenylamine hydrochloride in mixed diets was stable for 1 week if stored at 25°C. Formulated diets prepared at various times were analyzed for concentrations of 2-biphenylamine (Appendix K).

Clinical Examinations and Pathology

All animals were observed twice daily for morbidity or mortality. Clinical signs were recorded monthly. Body weights and feed consumption by cage were recorded every week for the first 13 weeks and monthly thereafter. The mean body weight per animal was calculated by dividing the total weight of all surviving animals in the group by the number of surviving animals in that group. Similarly, the average feed consumption per animal was calculated by dividing the total feed consumption of all animals in a group by the number of surviving animals in that 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 according to the procedures outlined in the 13-week study and in Table 1.

The pathology report and selected slides were evaluated by the NTP Pathology Working Group as described by Ward *et al.*, (1978). The diagnoses represent a consensus of contracting pathologists and the NTP Pathology Working Group.

Data Recording and Statistical Methods

Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart *et al.*, 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic

results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend.

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

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

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were fatal; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. 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 five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill period, and the terminal kill period. The denominators of these proportions were the numbers 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 (Peto *et al.*, 1980).

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

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

TABLE 1. EXPERIMENTAL DESIGN AND METHODS AND MATERIALS

	Single-Dose Study	14-Day Study	13-Week Study	2-Year Study
Experimental Design				
Size of Test Groups	2 males and 2 females of each species	5 males and 5 females of each species *(a)*	10 males and 10 females of each species	50 male and 49 female rats; 50 male and 50 female mice.
Doses	2-biphenylamine: 0.001, 0.01, 0.1, 1.0, or 10.0 g/kg body weight in corn oil by gavage	2-biphenylamine; 0, 1,000, 3,000, 10,000, or 30,000 ppm in feed 2-biphenylamine hydrochloride; 0, 400, 1,200, 3,600, 12,100, or 36,300 ppm in feed	2-biphenylamine: 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm in feed	2-biphenylamine hydrochloride: 0, 1,000, or 3,000 ppm in feed
Duration of Dosing	Single dose	14 days; killed on day 15	13 weeks; killed on day 91-92	103 weeks; killed at week 104-105
Type and Frequency of Observation	Observed daily for mortality and signs of toxicity; weighed on day 1, 7, and 14; killed on day 14.	Observed daily for mortality; weighed on days 1, 7, and 14.	Observed twice daily for mortality and signs of morbidity. Weekly clinical exam, including palpation for tissue masses or swelling. Weekly collection of data on body weight and feed consumption.	Observed twice daily for morbidity or mortality; clinical signs recorded monthly; body weights and feed consumption data (by cage) recorded weekly for 13 weeks, then monthly.
Necropsy and Histological Examination	Necropsies performed on all animals	Necropsies performed on all animals	Necropsies performed on all animals *(b,c)*	Necropsies performed on all animals *(b)*
Animals and Animal Maintenance				
Species	F344/N rats; B6C3F1 mice	F344/N rats; B6C3F1 mice	F344/N rats; B6C3F1 mice	F344/N rats; B6C3F1 mice
Animal Source	Frederick Cancer Research Center (Frederick, MD)	Frederick Cancer Research Center (Frederick, MD)	Frederick Cancer Research Center (Frederick, MD)	Harlan Industries (Indianapolis, IN)
Time Held Before Start of Test	1 week	2 weeks	1 week	2 weeks
Age When Placed on Study	6-7 weeks	6-7 weeks	5 weeks	6-7 weeks

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

	Single-Dose Study	14-Day Study	13-Week Study	2-Year Study
Method of Animal Distribution	Random	Assigned to test groups so that average cage weights approximately equal for all animals of same sex and species	Same as 14-day study	Assigned to individual cages according to table of random numbers; then cages assigned to control or dosed groups according to another table of random numbers
Feed	Wayne Lab Blox® meal, Allied Mills, Inc. (Chicago, IL). Available *ad libitum*	Same as single-dose study	Same as single-dose study	Same as single-dose study. Stainless steel feed containers changed weekly
Bedding	Aspen Bed®, American Excelsior (Baltimore, MD); Beta Chips® Agway Corp. (Syracuse, NY). Changed twice per week	Same as single-dose study	Same as single-dose study	Same as single-dose study
Water	Available in water bottles *ad libitum*, replaced twice per week	Same as single-dose study	Same as single-dose study	Tap water via Edstrom Automatic Watering System, Edstrom Industries (Waterford, WI)
Cages	Polycarbonate, Lab Products, Inc. (Garfield, NJ). Replaced twice per week	Same as single-dose study	Same as single-dose study	Same as single-dose study
Animals per Cage	2	5	5	5
Cage Filters	Nonwoven polyester filter sheets, Snow Filtration (Cincinnati, OH)	Same as single-dose study	Same as single-dose study	Same as single-dose study. Filters changed once every 2 weeks

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

	Single-Dose Study	14-Day Study	13-Week Study	2-Year Study
Animal Room Environment	Temperature, 17.2°-32.2°C. Humidity uncontrolled. Fluorescent lighting provided 12 hours per day.	Same as single-dose study	Same as single-dose study	Same as single-dose study
Other Chemicals on Test in same Room	None	None	None	None
Chemical/Feed Mixture	Single preparation	Prepared weekly by mixing test chemical and feed in Patterson-Kelly® Twin Shell Blender. Diets stored in dark at 4°C.	Same as single-dose study	Weighed amount of test chemical mixed with small amount of feed in aluminum vessel; premix and additional meal mixed for 20 min. in Patterson-Kelly® Twin Shell V-Blender (without intensifier bar). Diets stored in dark at 4°C

(a) Control groups for 2-biphenylamine contained 8 male and 9 female rats and 9 male and 8 female mice.

(b) Tissues examined: 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. Tissues preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

(c) Tissues examined only in control and high-dose groups. Blood samples were removed by orbital bleeding from all test animals at 1, 4, and 13 weeks; and hemoglobin, hematocrit, red blood cell, leucocytes, and neutrophil:lymphocyte ratio measured.

III. RESULTS

RATS

PRECHRONIC STUDIES

Single-Dose Study

Fourteen-Day Study with Technical-Grade 2-Biphenylamine

Fourteen-Day Study with 2-Biphenylamine Hydrochloride

Thirteen-Week Study with Technical-Grade 2-Biphenylamine

CHRONIC STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

Body Weights and Food Consumption

Survival

Pathology and Statistical Analyses of Results

MICE

PRECHRONIC STUDIES

Single-Dose Study

Fourteen-Day Study with Technical-Grade 2-Biphenylamine

Fourteen-Day Study with 2-Biphenylamine Hydrochloride

Thirteen-Week Study with Technical-Grade 2-Biphenylamine

CHRONIC STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

Body Weights and Food Consumption

Clinical Signs and Survival

Pathology and Statistical Analyses of Results

PRECHRONIC STUDIES

Single-Dose Study

Male and female rats receiving a single gavage dose of 10 g/kg technical-grade 2-biphenylamine died within a week following administration (Appendix L, Table L1).

Animals dosed with 0.1 and 1.0 g/kg exhibited lethargy during the first 24 hours, while those receiving 10.0 g/kg showed hyperexcitability followed by prostration and shallow breathing after administration (Appendix L, Table L2). All animals in the remaining dose groups (0.001, 0.01, 0.1, and 1.0 g/kg) had comparable weight gains during the 14-day observation period. Necropsy revealed lymph node enlargement in animals at all doses. Thickening of duodenal mucosa was observed in groups receiving 0.01 and 1.0 g/kg body weight of technical grade 2-biphenylamine.

Based on the results of this study, the dose levels of technical-grade 2-biphenylamine selected for use in the 14-day study were 0, 1,000, 3,000, 10,000, and 30,000 ppm in feed.

Fourteen-Day Study with Technical-Grade 2-Biphenylamine

Feeding diets containing 0, 1,000, 3,000, 10,000, or 30,000 ppm technical-grade 2-biphenylamine to male and female rats for 14 days did not result in any mortality. Although all experimental animal groups gained weight, there appeared to be a clear dose-related depression in mean body weight gain in both sexes of rats. Male and female rats receiving 30,000 ppm technical-grade 2-biphenylamine in feed showed mean body weight gain depression of 99.4% and 92.8% respectively, when compared with controls (Table 2).

Spleens with granular surface texture were observed in all rats dosed with technical-grade 2-biphenylamine. In addition, all male and female rats receiving 10,000 or 30,000 ppm of the chemical showed enlargement of the spleen (Table 3). Enlarged mesentric lymph nodes and hemorrhage of renal medulla were noted in all rats receiving 3,000 ppm or more of technical-grade 2-biphenylamine in feed.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING TECHNICAL-GRADE 2-BIPHENYLAMINE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Change Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Males					
0	8/8	89.6 ±5.40	152.1 ±3.73	+62.5 ±3.40	
1,000	5/5	92.0 ±5.28	145.2 ±7.12	+53.2 ±1.98	-14.9
3,000	5/5	93.8 ±4.18	143.4 ±4.60	+49.6 ±1.96	-20.6
10,000	5/5	98.6 ±5.23	128.6 ±5.25	+30.0 ±1.76	-52.0
30,000	5/5	97.4 ±3.43	97.8 ±5.35	+ 0.4 ±3.66	-99.4
Females					
0	9/9	78.4 ±2.34	117.1 ±2.05	+38.7 ±1.05	
1,000	5/5	80.6 ±4.49	120.6 ±4.17	+40.0 ±1.38	+ 3.4
3,000	5/5	79.2 ±3.10	112.6 ±2.64	+33.4 ±1.03	-13.7
10,000	5/5	80.8 ±4.50	93.8 ±6.26	+13.0 ±2.43	-66.4
30,000	5/5	79.6 ±3.40	82.4 ±4.45	+ 2.8 ±1.91	-92.8

(a) Number surviving/number in the group.

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

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

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

Fourteen-Day Study with 2-Biphenylamine Hydrochloride

The survival and body weight changes for rats of both sexes receiving diets containing 0, 400, 1,200, 3,600, 12,100, or 36,300 ppm 2-biphenylamine hydrochloride are shown in Table 4. All animals survived to the end of the study. Both male and female rats receiving 12,100 or 36,300 ppm of the chemical showed decreased body weight gains when compared with controls. The highest depression in weight gain was observed in the groups receiving 36,300 ppm 2-biphenylamine hydrochloride. At this dose level, weight change relative to controls was -70.6% and -55.4% for males and females, respectively.

The incidences of splenomegaly in both male and female rats receiving 2-biphenylamine hydrochloride are shown in Table 3. In males, three animals had splenomegaly, one in the group receiving 1,200 ppm of the chemical and two in the group receiving 36,300 ppm. In females, three animals had splenomegaly, one in

TABLE 3. INCIDENCE OF SPLENIC ENLARGEMENT IN RATS FED DIETS CONTAINING TECHNICAL-GRADE 2-BIPHENYLAMINE OR 2-BIPHENYLAMINE HYDROCHLORIDE FOR 14 DAYS

Compound	Dose (ppm)	Males	Females
Technical-Grade	0	0/5	0/5
2-Biphenylamine	1,000	0/5	0/5
	3,000	0/5	0/5
	10,000	5/5	5/5
	30,000	5/5	5/5
2-Biphenylamine	0	0/5	0/5
Hydrochloride	400	0/5	0/5
	1,200	1/5	1/5
	3,600	0/5	0/5
	12,100	0/5	1/5
	36,300	2/5	1/5

each of the groups receiving 1,200, 12,100, or 36,300 ppm 2-biphenylamine hydrochloride. The incidence of splenomegaly is higher in animals given technical-grade 2-biphenylamine than in animals given 2-biphenylamine hydrochloride.

2-Biphenylamine hydrochloride appeared to be less toxic than technical-grade 2-biphenylamine as evidenced by the lower incidence of splenomegaly (Table 3) and lower decrements in body weight gain relative to controls (Tables 2 and 4).

Thirteen-Week Study with Technical Grade 2-Biphenylamine

Survival and body weight changes of male and female rats fed diets containing 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm of technical-grade 2-biphenylamine are shown in Table 5. One male rat from the group receiving 300 ppm and five female rats receiving 30,000 ppm died on day 26. All five females were from the same cage and were found dead on the same day, suggesting that the deaths were not chemical-related. The data indicate compound-related depression in the mean body weight gains. The maximum depression in body weight gain relative to controls was observed at 30,000 ppm, amounting to 47.6% for males and 38.9% for females.

The hematological data are presented in Table 6. Significant ($P < 0.001$) dose-related decreases in hemoglobin concentration and red blood cells were observed in both male and female rats examined at weeks 1, 4, and 13. Leucocyte count was markedly ($P < 0.001$) increased in both male and female rats at weeks 1 and 4, but this trend had diminished somewhat by week 13. This diminishing trend in leucocyte count with time may be due to activation of a hemeostatic mechanism in these animals. Hematocrit levels showed no consistent effect, although there was some evidence of a dose-related decrease in female rats at week 1 ($P < 0.05$) and week 13 ($P < 0.001$).

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Change Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Male					
0	5/5	129.6±2.42	186.0±3.42	+56.4±1.54	
400	5/5	130.4±4.19	185.6±4.13	+55.2±1.80	- 2.1
1,200	5/5	129.4±3.50	187.2±5.61	+57.8±2.56	+ 2.5
3,600	5/5	129.6±2.91	186.8±3.35	+57.2±2.35	+ 1.4
12,100	5/5	129.6±2.84	175.8±5.91	+46.2±3.38	-18.1
36,300	5/5	129.6±2.86	146.2±3.75	+16.6±2.80	-70.6
Female					
0	5/5	103.0±2.28	132.6±3.06	+29.6±1.21	
400	5/5	103.2±2.56	132.6±3.17	+29.4±1.44	- 0.7
1,200	5/5	103.2±2.71	135.6±3.71	+32.4±2.14	+ 9.5
3,600	5/5	103.2±2.58	132.4±4.23	+29.2±1.66	- 1.4
12,100	5/5	103.0±2.61	131.4±3.83	+28.4±1.94	- 4.1
36,300	5/5	103.0±2.51	116.2±1.43	+13.2±1.36	-55.4

(a) Number surviving/number in the group.

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

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

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

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING TECHNICAL-GRADE 2-BIPHENYLAMINE FOR 13 WEEKS

Dose (ppm)	Survival *(a)* (Day of Death)	Mean Body Weight (grams)			Weight Change Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Male					
0	10/10	83.2±3.65	305.1±9.07	+221.9±7.20	
300	9/10 (26)	85.3±3.11	302.2±6.60	+216.9±5.77	- 2.3
1,000	10/10	83.2±3.72	305.0±5.81	+221.8±5.57	0.0
3,000	10/10	83.1±3.82	297.2±4.23	+214.1±6.54	- 3.5
10,000	10/10	83.1±3.74	281.3±4.07	+198.2±4.48	-10.7
30,000	10/10	83.1±3.49	199.3±3.78	+116.2±4.09	-47.6
Female					
0	10/10	69.9±2.07	190.0±3.58	+120.1±4.51	
300	10/10	70.0±2.31	185.6±1.94	+115.6±2.90	- 3.7
1,000	10/10	70.0±2.29	182.8±3.20	+112.8±3.13	- 6.1
3,000	10/10	70.0±2.25	176.4±3.14	+106.4±3.06	-11.4
10,000	10/10	70.0±2.06	178.9±5.38	+108.9±4.96	- 9.3
30,000	5/10 (26) *(d)*	72.6±3.72	146.0±3.86	+ 73.4±2.23	-38.9

(a) Number surviving/number in the group.

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

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

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

(d) All five animals were from the same cage and were found dead on the same day.

TABLE 6. SUMMARY OF HEMATOLOGY DATA ON RATS FED DIETS CONTAINING TECHNICAL GRADE 2-BIPHENYLAMINE FOR 13 WEEKS *(a)*

Determination	Dose (ppm)	Weeks on Study: 1 — Males *(b)*	1 — Females *(c)*	4 — Males *(b)*	4 — Females *(c)*	13 — Males *(b)*	13 — Females *(c)*
Hemoglobin	0	14.2 ± 0.2	15.0 ± 0.3	15.9 ± 0.3	16.9 ± 0.2	18.8 ± 0.3	16.3 ± 0.3
(g/100 ml)	300	14.4 ± 0.6	14.2 ± 0.4	16.6 ± 0.3	17.2 ± 0.2	17.8 ± 0.4	16.8 ± 0.4
	1,000	13.6 ± 0.3	14.3 ± 0.2	16.2 ± 0.3	16.9 ± 0.2	18.9 ± 0.5	15.8 ± 0.2
	3,000	13.7 ± 0.5	14.2 ± 0.2	13.5 ± 0.2 *(d)*	14.8 ± 0.3 *(d)*	17.4 ± 0.3 *(d)*	15.0 ± 0.2 *(d)*
	10,000	12.9 ± 0.3 *(d)*	12.8 ± 0.4 *(d)*	14.3 ± 0.3 *(d)*	16.0 ± 0.6 *(d)*	17.3 ± 0.3 *(d)*	15.1 ± 0.3 *(e)*
	30,000	13.0 ± 0.2 *(d)*	13.2 ± 0.3 *(d)*	13.2 ± 0.4 *(d)*	14.8 ± 0.2 *(d)*	15.5 ± 0.5 *(d)*	13.8 ± 0.1 *(d)*
	Dose-Response	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
Hematocrit (%)	0	36.6 ± 0.7	40.5 ± 0.6	38.9 ± 0.7	45.2 ± 1.3	45.7 ± 1.1	41.7 ± 0.6
	300	39.7 ± 1.7	41.5 ± 2.7	38.9 ± 1.0	43.5 ± 0.8	45.9 ± 0.9	46.3 ± 1.9
	1,000	38.1 ± 0.9	40.4 ± 1.8	41.5 ± 2.4	45.6 ± 0.9	46.8 ± 1.7	41.6 ± 1.4
	3,000	37.5 ± 1.7	37.9 ± 0.9	35.2 ± 0.6	37.5 ± 0.9	43.7 ± 0.9	41.0 ± 2.1
	10,000	36.5 ± 1.0	36.0 ± 1.3 *(e)*	39.1 ± 0.6	43.3 ± 1.5	46.3 ± 1.0	39.0 ± 0.8 *(e)*
	30,000	36.0 ± 0.5	38.5 ± 1.0	38.3 ± 1.3	44.7 ± 3.1	43.2 ± 1.9	37.1 ± 1.2 *(d)*
	Dose-Response	NS	P<0.05	NS	NS	NS	P<0.001
Red Blood Cell *(f)*	0	5.96 ± .11	6.30 ± .08	6.84 ± .07	7.30 ± .09	6.38 ± .14	6.02 ± .07
(10^6/mm^3)	300	6.23 ± .23	6.44 ± .38	6.93 ± .15	7.47 ± .11	6.16 ± .17	6.49 ± .22
	1,000	5.89 ± .13	6.15 ± .11	6.81 ± .35	7.46 ± .10	6.27 ± .30	6.08 ± .16
	3,000	5.99 ± .23	6.21 ± .20	5.73 ± .10 *(d)*	6.14 ± .13 *(d)*	6.01 ± .14	5.70 ± .20
	10,000	5.35 ± .22 *(d)*	4.95 ± .16 *(d)*	6.00 ± .13 *(d)*	6.47 ± .17 *(d)*	6.38 ± .15	5.43 ± .15 *(d)*
	30,000	4.27 ± .10 *(d)*	3.79 ± .09 *(d)*	3.94 ± .12 *(d)*	4.37 ± .11 *(d)*	4.70 ± .14 *(d)*	4.71 ± .10 *(d)*
	Dose-Response	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
Leucocytes	0	6.71 ± .39	7.28 ± 0.45	9.51 ± 1.32	9.65 ± 0.33	10.95 ± 0.93	7.43 ± 0.84
(10^3/mm^3)	300	8.16 ± 1.40	7.21 ± 0.48	15.91 ± 3.70	11.18 ± 0.70	14.04 ± 1.52	11.94 ± 2.52
	1,000	9.96 ± 1.38 *(e)*	8.81 ± 1.35	9.33 ± 1.41	11.51 ± 1.20	11.39 ± 0.63	9.12 ± 0.90
	3,000	10.59 ± 1.45 *(d)*	7.59 ± 0.47	12.21 ± 1.10	13.18 ± 1.01 *(d)*	12.96 ± 1.17	10.25 ± 0.70 *(e)*
	10,000	16.59 ± 1.27 *(d)*	17.07 ± 2.45 *(d)*	9.92 ± 0.60	11.83 ± 0.95 *(e)*	13.03 ± 1.30	10.49 ± 0.87 *(e)*
	30,000	75.67 ± 5.63 *(d)*	84.80 ± 5.31 *(d)*	47.27 ± 5.58 *(d)*	70.31 ± 5.21 *(d)*	19.48 ± 2.10 *(d)*	11.11 ± 2.08 *(e)*
	Dose-Response	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
Neutrophil/	0	21/77	22/77	15/84	21/79	15/85	9/91
Lymphocyte (%)	300	30/69	21/77	24/75	29/69	17/82	13/86
	1,000	23/76	26/74	20/80	29/69	17/82	13/86
	3,000	22/77	20/79	18/82	15/84	12/88	12/88
	10,000	18/82	23/76	11/88	14/86	15/85	11/88
	30,000	22/76	15/84	16/82	16/84	13/85	12/87

(a) Values presented include the mean ± standard error.

(b) Mean values for each sample period are based on orbital bleedings of 10 animals in the control, 1,000-ppm, 3,000-ppm, 10,000-ppm, and 30,000-ppm groups. For the 300-ppm group, 10 animals were bled at week 1, and 9 animals were bled at weeks 4 and 13.

(c) Mean values for each sample period are based on orbital bleedings of 10 animals in the control, 300-ppm, 1,000-ppm, 3,000-ppm, and 10,000-ppm groups. For the 30,000-ppm group, 10 animals were bled at weeks 1 and 4, and 5 animals were bled at week 13.

(d) $P < 0.01$ vs. controls.

(e) $P < 0.05$ vs. controls.

(f) For red blood cell determinations, two samples per animal were analyzed.

Splenomegaly was observed in all rats fed 30,000 ppm and in 8/10 males and 2/10 females fed 10,000 ppm. Spleens of rats fed 3,000 ppm were not enlarged. Hemosiderosis, congestion, and extramedullary hematopoiesis were found in the spleens of 9/10 or 10/10 of each group of rats receiving 3,000 ppm or more and in females receiving 1,000 ppm or more of 2-biphenylamine (Table 7).

Erythroid hyperplasia of the bone marrow was observed in 2/10 males and 6/10 females receiving 10,000 ppm and in all males and 4/5 females receiving 30,000 ppm.

Renal effects in rats receiving 30,000 ppm technical-grade 2-biphenylamine included cystic tubular degeneration and papillary necrosis (9/10 or 10/10 rats of each sex), interstitial fibrosis (all males and 4/10 females), and chronic nephritis (all males and 4/10 females). Transitional-cell hyperplasia of the urinary bladder was observed in 3/10 males and 3/10 females receiving 30,000 ppm (Table 7).

The 14-day study indicated that the 2-biphenylamine hydrochloride was less toxic than technical-grade 2-biphenylamine, as evidenced by the decreased incidence of splenomegaly and lesser depression of weight gain relative to controls (Tables 2, 3, and 4). From these results, the Bioassay Program concluded that the histopathologic and hematologic effects of 2-biphenylamine hydrochloride would be less severe than those observed with technical grade 2-biphenylamine in the 13-week study. This conclusion led to the selection of 1,000 and 3,000 ppm as dose levels of 2-biphenylamine hydrochloride for use in the chronic study.

TABLE 7. INCIDENCE OF HISTOPATHOLOGIC EFFECTS IN RATS FED DIETS CONTAINING TECHNICAL-GRADE 2-BIPHENYLAMINE FOR 13 WEEKS

	Dose (ppm)											
	0		300		1,000		3,000		10,000		30,000	
Site and Effect:	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Spleen:												
Congestion	0/10	0/10	0/10	0/10	7/10	10/10	10/10	10/10	10/10	9/10	10/10	10/10
Thickened Capsule	0/10	0/10	0/10	0/10	2/10	0/10	5/10	4/10	10/10	10/10	9/10	10/10
Extramedullary Hematopoiesis	0/10	0/10	0/10	0/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Lymphoid Atrophy	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	2/10	9/10	6/10
Hemosiderosis	0/10	0/10	0/10	0/10	1/10	10/10	10/10	10/10	10/10	10/10	9/10	10/10
Kidney:												
Cystic Tubular Degeneration	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	10/10	10/10
Interstitial Fibrosis	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	10/10	4/10
Pigment	0/10	0/10	0/10	0/10	0/10	0/10	2/10	0/10	5/10	1/10	10/10	10/10
Papillary Necrosis	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	9/10	10/10
Mineralization	0/10	0/10	0/10	0/10	0/10	0/10	0/10	4/10	0/10	2/10	9/10	10/10
Chronic Nephritis	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	10/10	4/10
Transitional-Cell Hyperplasia (Pelvis)	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	5/10
Liver:												
Pigment	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	8/10	9/10
Hemopoietic Foci	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	7/10	2/10
Testis:												
Focal Tubular Degeneration	0/10		0/10		0/10		2/10		4/10		9/10	
Stomach:												
Hyperkeratosis	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10	5/10	8/10
Acanthosis	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	2/10	0/10	0/10
Bone Marrow:												
Erythroid Hyperplasia	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	2/10	6/10	9/9	4/5
Peripheral Blood:												
Polychromasia	0/10	0/10	0/10	0/10	0/10	0/10	10/10	10/10	10/10	10/10	10/10	10/10
Anisocytosis	0/10	0/10	0/10	0/10	0/10	0/10	9/10	10/10	10/10	10/10	10/10	10/10
Poikilocytosis	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	9/10	6/10	10/10	10/10
Howell-Jolly Bodies	0/10	0/10	0/10	0/10	0/10	0/10	1/10	0/10	6/10	9/10	8/10	8/10
Target Cells	0/10	0/10	0/10	0/10	0/10	0/10	4/10	4/10	9/10	10/10	10/10	10/10
Urinary Bladder:												
Transitional-Cell Hyperplasia	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	3/10	3/10
Mucosal Thickening	0/10	0/10	0/10	0/10	0/10	0/10	1/10	1/10	4/10	3/10	3/10	2/10

CHRONIC STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

Body Weights and Food Consumption

After week 22, mean body weights of high-dose rats of either sex and of low-dose male rats were slightly lower than those of the controls (Figure 1 and Table 8). The average daily feed consumption per rat in low- and high-dose groups was 95% (21.1/22.3) and 92% (20.5/22.3) that of controls for males and 95% (17.6/18.5) and 80% (14.8/18.5) for females (Appendix M, Tables M1 and M2). No compound-related clinical signs were observed.

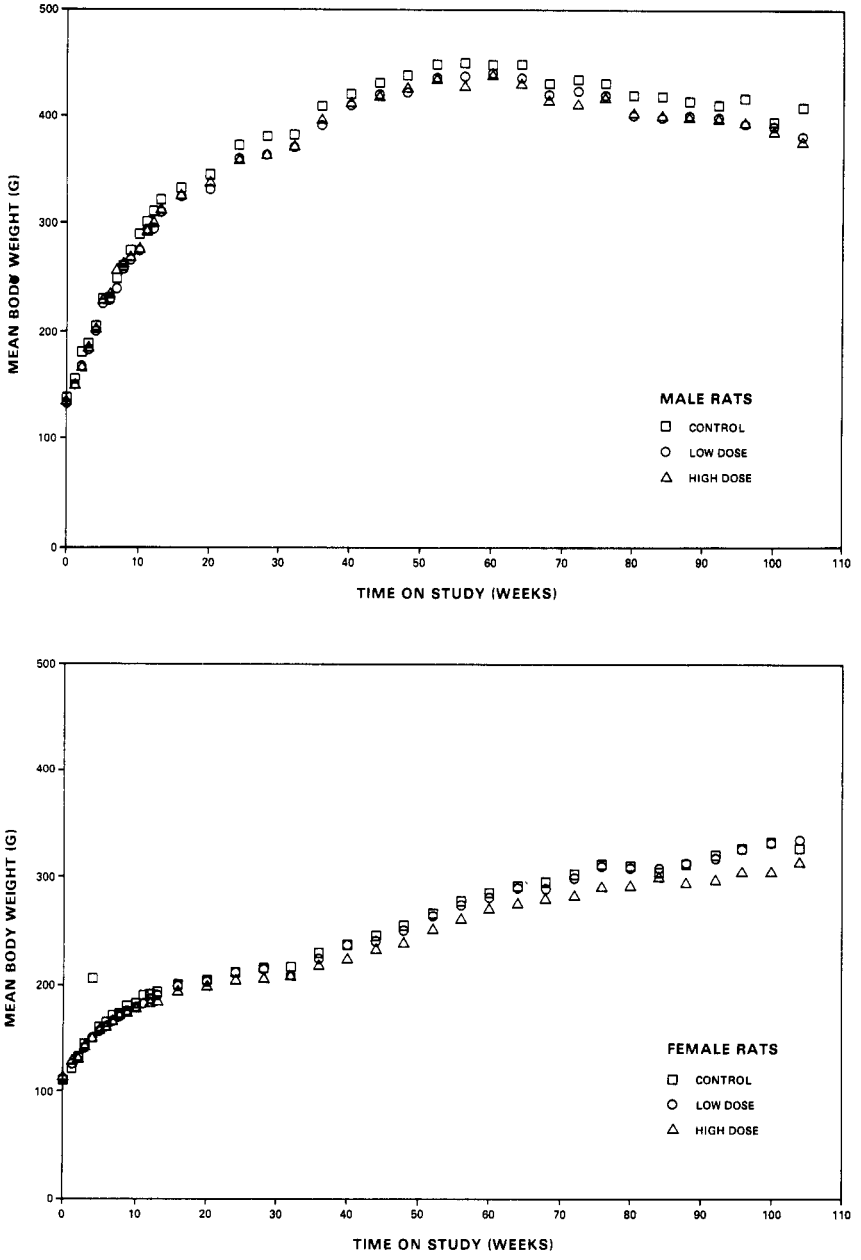

Figure 1. Growth Curves for Rats Fed Diets Containing 2-Biphenylamine Hydrochloride

TABLE 8. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF RATS FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE FOR 2 YEARS

		Cumulative Mean Body Weight Change (grams)			Weight Change Relative to Controls *(a)* (Percent)	
	Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males	0	137 *(b)*	133 *(b)*	135 *(b)*		
	3	50	50	50	0	0
	24	235	224	221	- 5	- 6
	44	296	287	283	- 3	- 4
	64	313	304	296	- 3	- 5
	84	282	264	266	- 6	- 6
	104	271	246	240	- 9	-11
	Final Body Weights	408	379	375	- 7 *(c)*	- 8 *(c)*
Females	0	109 *(b)*	110 *(b)*	114 *(b)*		
	3	35	29	27	-17	-23
	24	104	103	91	- 1	-13
	44	137	130	120	- 5	-12
	64	183	179	162	- 2	-11
	84	195	197	183	+ 1	- 6
	104	217	224	200	+ 3	- 8
	Final Body Weights	326	334	314	+ 2 *(c)*	- 4 *(c)*

(a) Weight change relative to controls =

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

(b) Initial weight

(c) Final body weight relative to controls (percent)

Survival

Probability estimates of survival of male and female rats fed diets containing 0, 1,000, or 3,000 ppm 2-biphenylamine hydrochloride are shown in Figure 2. No significant differences in survival were observed between any group of either sex of rats. In male rats, two control, three low-dose, and one high-dose animal died of natural causes during weeks 104-105. In the statistical analysis, no distinction was made between these animals and those killed during this terminal kill period. One of the 50 low-dose animals initially placed in the study as a female was discovered to be a male and was eliminated from the study.

In male rats, 36/50 (72%) of the controls, 42/50 (84%) of the low-dose, and 40/50 (80%) of the high-dose group lived to the end of the study (104-105 weeks). In female rats, 38/50 (76%) of the controls, 42/49 (86%) of the low-dose, and 43/50 (86%) of the high-dose group lived to the end of the study (105-106 weeks).

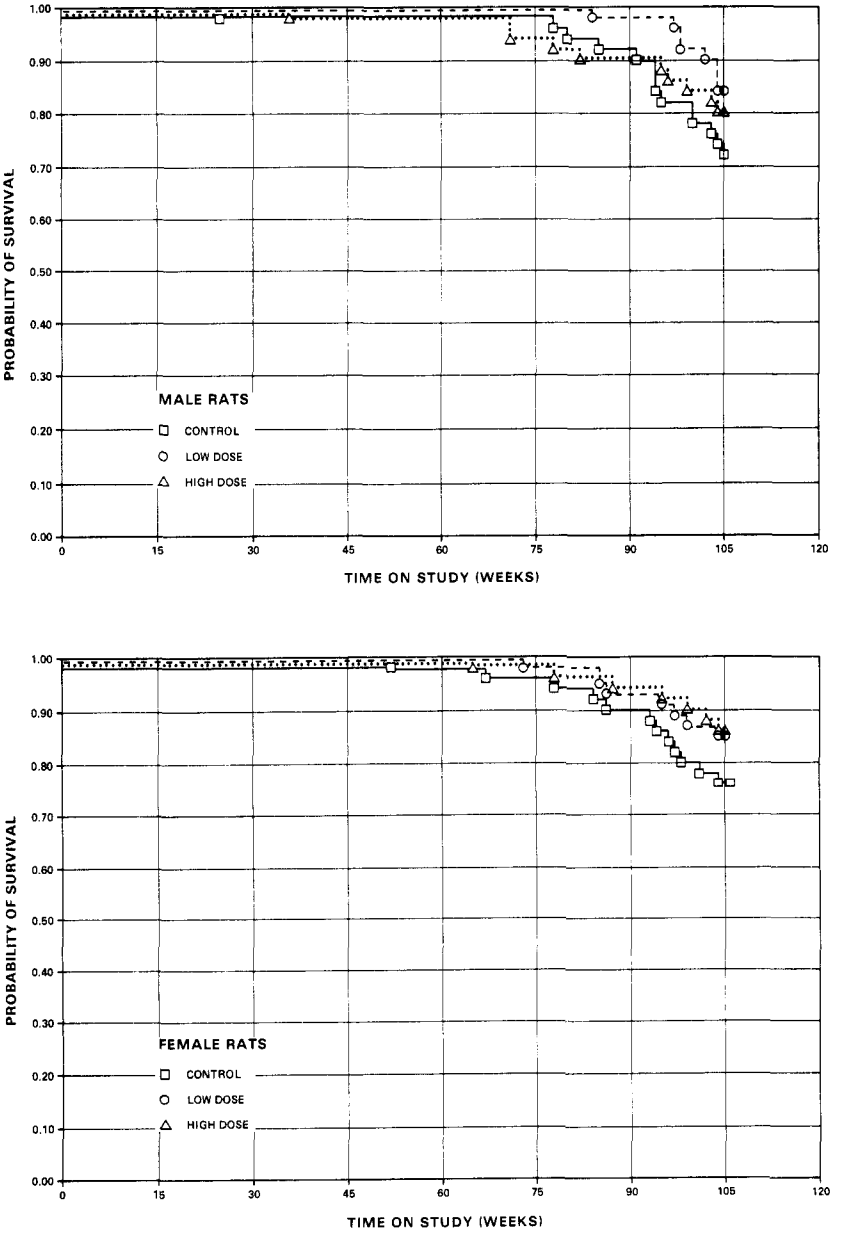

Figure 2. Survival Curves for Rats Fed Diets Containing 2-Biphenylamine Hydrochloride

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2. The survival and tumor status for each individual animal are given in Tables A3 and A4. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Statistical analyses of primary tumor incidence in the various dose groups are shown in Tables 10 and 11.

Kidney: Renal changes occurred in most of the dosed and control male rats. The incidence of interstitial fibrosis and inflammatory cells was highest in dosed male rats (Table 9).

Hematopoietic System: The incidence of leukemia in male and female control rats was greater than that observed in the groups receiving 2-biphenylamine hydrochloride. In male control rats, the incidence was 15/50 (30%), compared with 1/50 (2%) and 4/50 (8%) in the low- and high-dose groups, respectively. In control females, the incidence was 5/50 (10%), compared with 1/49 (2%) and 2/50 (4%) in the low- and high-dose groups, respectively. The differences in leukemia incidence were not statistically significant.

Mammary Gland: Fibroadenomas or adenomas in the mammary gland of female rats occurred at a higher incidence ($P \leq 0.010$) in the control group than in either dosed group: 22/50, 44%, in the controls, 10/49, 20%, in the low-dose, and 10/50, 20%, in the high-dose group.

TABLE 9. INCIDENCE OF RATS WITH NONNEOPLASTIC LESIONS OF THE KIDNEY IN THE 2-YEAR STUDY

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Number of Kidneys Evaluated	49	50	50	50	49	50
Nephropathy	46	50	49	26	37	43
Inflammation	21	43	41	4	5	6
Interstitial Fibrosis	15	41	40	0	2	6

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

	Control	Low Dose	High Dose
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(b)*	6/50 (12%)	2/50 (4%)	4/50 (8%)
Adjusted *(c)*	14.0%	4.4%	9.2%
Terminal *(d)*	3/38 (8%)	2/45 (4%)	2/41 (5%)
Statistical Tests *(e)*			
Life Table	P=0.395N	P=0.101N	P=0.349N
Incidental Tumor Test	P=0.571N	P=0.187N	P=0.588N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.405N	P=0.134N	P=0.370N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	4/49 (8%)	2/50 (4%)
Adjusted *(c)*	5.0%	8.9%	4.8%
Terminal *(d)*	1/38 (3%)	4/45 (9%)	1/41 (2%)
Statistical Tests *(e)*			
Life Table	P=0.518N	P=0.417	P=0.666N
Incidental Tumor Test	P=0.586N	P=0.360	P=0.610
Cochran-Armitage Trend, Fisher Exact Tests	P=0.536N	P=0.329	P=0.691
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	4/49 (8%)	3/50 (6%)
Adjusted *(c)*	5.0%	8.9%	7.1%
Terminal *(d)*	1/38 (3%)	4/45 (9%)	2/41 (5%)
Statistical Tests *(e)*			
Life Table	P=0.521	P=0.417	P=0.533
Incidental Tumor Test	P=0.457	P=0.360	P=0.420
Cochran-Armitage Trend, Fisher Exact Tests	P=0.502	P=0.329	P=0.500
Hematopoietic System: Myelomonocytic Leukemia			
Tumor Rates			
Overall *(b)*	14/50 (28%)	1/50 (2%)	4/50 (8%)
Adjusted *(c)*	32.8%	2.0%	9.5%
Terminal *(d)*	10/38 (26%)	0/45 (0%)	3/41 (7%)
Statistical Tests *(e)*			
Life Table	P=0.013N	P<0.001N	P=0.009N
Incidental Tumor Test	P=0.028N	P<0.001N	P=0.018N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.013N	P<0.001N	P=0.009N
Hematopoietic System: All Leukemia			
Tumor Rates			
Overall *(b)*	15/50 (30%)	1/50 (2%)	4/50 (8%)
Adjusted *(c)*	34.5%	2.0%	9.5%
Terminal *(d)*	10/38 (26%)	0/45 (0%)	3/41 (7%)
Statistical Tests *(e)*			
Life Table	P=0.008N	P<0.001N	P=0.005N
Incidental Tumor Test	P=0.018N	P<0.001N	P=0.012N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.007N	P<0.001N	P=0.005N

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

	Control	Low Dose	High Dose
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	16/45 (36%)	17/45 (38%)	13/48 (27%)
Adjusted *(c)*	41.0%	39.4%	30.1%
Terminal *(d)*	15/38 (39%)	14/40 (35%)	10/40 (25%)
Statistical Tests *(e)*			
Life Table	P=0.230N	P=0.569	P=0.276N
Incidental Tumor Test	P=0.224N	P=0.512	P=0.273N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.194N	P=0.500	P=0.255N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	12/48 (25%)	12/50 (24%)	8/49 (16%)
Adjusted *(c)*	29.0%	26.7%	19.5%
Terminal *(d)*	9/38 (24%)	12/45 (27%)	8/41 (20%)
Statistical Tests *(e)*			
Life Table	P=0.155N	P=0.415N	P=0.184N
Incidental Tumor Test	P=0.202N	P=0.504N	P=0.267N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.172N	P=0.547N	P=0.211N
Adrenal: Pheochromocytoma or Pheochromocytoma Malignant			
Tumor Rates			
Overall *(b)*	12/48 (25%)	13/50 (26%)	8/49 (16%)
Adjusted *(c)*	29.0%	28.9%	19.5%
Terminal *(d)*	9/38 (24%)	13/45 (29%)	8/41 (20%)
Statistical Tests *(e)*			
Life Table	P=0.144N	P=0.499N	P=0.184N
Incidental Tumor Test	P=0.189N	P=0.589N	P=0.267N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.162N	P=0.547	P=0.211N
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	2/47 (4%)	7/49 (14%)	1/46 (2%)
Adjusted *(c)*	5.3%	15.9%	2.6%
Terminal *(d)*	2/38 (5%)	7/44 (16%)	1/39 (3%)
Statistical Tests *(e)*			
Life Table	P=0.268N	P=0.120	P=0.491N
Incidental Tumor Test	P=0.268N	P=0.120	P=0.491N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.282N	P=0.090	P=0.508N
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/47 (6%)	7/49 (14%)	2/46 (4%)
Adjusted *(c)*	8.0%	15.9%	5.1%
Terminal *(d)*	3/38 (8%)	7/44 (16%)	2/39 (5%)
Statistical Tests *(e)*			
Life Table	P=0.313N	P=0.223	P=0.488N
Incidental Tumor Test	P=0.313N	P=0.223	P=0.488N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.330N	P=0.176	P=0.510N

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

	Control	Low Dose	High Dose
Pancreatic Islets: Islet-Cell Adenoma			
Tumor Rates			
Overall*(b)*	4/48 (8%)	4/50 (8%)	4/47 (9%)
Adjusted *(c)*	10.5%	8.9%	9.1%
Terminal *(d)*	4/38 (11%)	4/45 (9%)	2/41 (5%)
Statistical Tests *(e)*			
Life Table	P=0.578N	P=0.548N	P=0.610N
Incidental Tumor Test	P=0.527	P=0.548N	P=0.548
Cochran-Armitage Trend, Fisher Exact Tests	P=0.578	P=0.619N	P=0.631
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(b)*	4/50 (8%)	0/50 (0%)	1/50 (2%)
Adjusted *(c)*	10.5%	0.0%	2.4%
Terminal *(d)*	4/38 (11%)	0/45 (0%)	1/41 (2%)
Statistical Tests *(e)*			
Life Table	P=0.152N	P=0.044N	P=0.157N
Incidental Tumor Test	P=0.152N	P=0.044N	P=0.157N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.165N	P=0.059N	P=0.181N
Mammary Gland: Fibroadenoma or Adenoma			
Tumor Rates			
Overall *(b)*	4/50 (8%)	0/50 (0%)	2/50 (4%)
Adjusted *(c)*	10.5%	0.0%	4.9%
Terminal *(d)*	4/38 (11%)	0/45 (0%)	2/41 (5%)
Statistical Tests *(e)*			
Life Table	P=0.351N	P=0.044N	P=0.302N
Incidental Tumor Test	P=0.351N	P=0.044N	P=0.302N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.369N	P=0.059N	P=0.339N
Preputial Gland: Adenoma			
Tumor Rates			
Overall *(b)*	8/50 (16%)	4/50 (8%)	4/50 (8%)
Adjusted *(c)*	20.2%	8.6%	9.4%
Terminal *(d)*	7/38 (18%)	3/45 (7%)	3/41 (7%)
Statistical Tests *(e)*			
Life Table	P=0.164N	P=0.116N	P=0.151N
Incidental Tumor Test	P=0.224N	P=0.172N	P=0.211N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.179N	P=0.178N	P=0.178N
Preputial Gland: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	8/50 (16%)	4/50 (8%)	5/50 (10%)
Adjusted *(c)*	20.2%	8.6%	17.0%
Terminal *(d)*	7/38 (18%)	3/45 (7%)	4/41 (10%)
Statistical Tests *(e)*			
Life Table	P=0.269N	P=0.116N	P=0.237N
Incidental Tumor Test	P=0.346N	P=0.172N	P=0.312N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.291N	P=0.178N	P=0.277N

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

	Control	*Low* Dose	*High* Dose
Testis: Interstitial-Cell Tumor			
Tumor Rates			
Overall *(b)*	47/49 (96%)	50/50 (100%)	45/49 (92%)
Adjusted *(c)*	100.0%	100.0%	100.0%
Terminal *(d)*	38/38 (100%)	45/45 (100%)	40/40 (100%)
Statistical Tests *(e)*			
Life Table	P=0.218N	P=0.153N	P=0.208N
Incidental Tumor Test	P=0.247N	P=0.718	P=0.335N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.156N	P=0.242	P=0.339N

(a) Dosed groups received doses of 1,000 or 3,000 ppm of 2-biphenylamine hydrochloride in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at the end of the study.
(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 before the end of the study as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

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

	Control	Low Dose	High Dose
Hematopoietic System: Myelomonocytic Leukemia			
Tumor Rates			
Overall *(b)*	4/50 (8%)	1/49 (2%)	2/50 (4%)
Adjusted *(c)*	9.4%	2.4%	4.7%
Terminal *(d)*	2/38 (5%)	1/42 (2%)	2/43 (5%)
Statistical Tests *(e)*			
Life Table	P=0.305N	P=0.162N	P=0.296N
Incidental Tumor Test	P=0.375N	P=0.197N	P=0.394N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.338N	P=0.187N	P=0.339N
Hematopoietic System: All Leukemia			
Tumor Rates			
Overall *(b)*	5/50 (10%)	1/49 (2%)	2/50 (4%)
Adjusted *(c)*	11.3%	2.4%	4.7%
Terminal *(d)*	2/38 (5%)	1/42 (2%)	2/43 (5%)
Statistical Tests *(e)*			
Life Table	P=0.196N	P=0.095N	P=0.190N
Incidental Tumor Test	P=0.243N	P=0.144N	P=0.262N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.218N	P=0.107N	P=0.218N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	5/50 (10%)	1/49 (2%)	3/50 (6%)
Adjusted *(c)*	11.3%	2.4%	6.8%
Terminal *(d)*	2/38 (5%)	1/42 (2%)	2/43 (5%)
Statistical Tests *(e)*			
Life Table	P=0.353N	P=0.095N	P=0.313N
Incidental Tumor Test	P=0.447N	P=0.144N	P=0.446N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.390N	P=0.107N	P=0.357N
Liver: Neoplastic Nodule			
Tumor Rates			
Overall *(b)*	1/50 (2%)	5/49 (10%)	1/50 (2%)
Adjusted *(c)*	2.5%	11.6%	2.3%
Terminal *(d)*	0/38 (0%)	4/42 (10%)	1/43 (2%)
Statistical Tests *(e)*			
Life Table	P=0.411N	P=0.131	P=0.734N
Incidental Tumor Test	P=0.490N	P=0.077	P=0.716
Cochran-Armitage Trend, Fisher Exact Tests	P=0.457N	P=0.098	P=0.753
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	33/47 (70%)	38/48 (79%)	38/50 (76%)
Adjusted *(c)*	76.7%	86.3%	80.8%
Terminal *(d)*	27/37 (73%)	35/41 (85%)	34/43 (79%)
Statistical Tests *(e)*			
Life Table	P=0.501N	P=0.456	P=0.567N
Incidental Tumor Test	P=0.440	P=0.270	P=0.394
Cochran-Armitage Trend, Fisher Exact Tests	P=0.370	P=0.221	P=0.339

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

	Control	Low Dose	High Dose
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	0/49 (0%)	3/50 (6%)
Adjusted *(c)*	5.3%	0.0%	6.7%
Terminal *(d)*	2/38 (5%)	0/42 (0%)	2/43 (5%)
Statistical Tests *(e)*			
Life Table	P=0.350	P=0.217N	P=0.553
Incidental Tumor Test	P=0.309	P=0.217N	P=0.495
Cochran-Armitage Trend, Fisher Exact Tests	P=0.315	P=0.253N	P=0.500
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	2/49 (4%)	4/47 (9%)	1/49 (2%)
Adjusted *(c)*	5.4%	9.8%	2.3%
Terminal *(d)*	2/37 (5%)	4/41 (10%)	1/43 (2%)
Statistical Tests *(e)*			
Life Table	P=0.285N	P=0.385	P=0.448N
Incidental Tumor Test	P=0.285N	P=0.385	P=0.448N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.337N	P=0.319	P=0.500N
Thyroid: C-Cell Carcinoma			
Tumor Rates			
Overall *(b)*	3/49 (6%)	1/47 (2%)	2/49 (4%)
Adjusted *(c)*	8.1%	2.4%	4.7%
Terminal *(d)*	3/37 (8%)	1/41 (2%)	2/43 (5%)
Statistical Tests *(e)*			
Life Table	P=0.443N	P=0.269N	P=0.431N
Incidental Tumor Test	P=0.443N	P=0.269N	P=0.432N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.496N	P=0.324N	P=0.500N
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	5/49 (10%)	5/47 (11%)	3/49 (6%)
Adjusted *(c)*	13.5%	12.2%	7.0%
Terminal *(d)*	5/37 (14%)	5/41 (12%)	3/43 (7%)
Statistical Tests *(e)*			
Life Table	P=0.223N	P=0.565N	P=0.276N
Incidental Tumor Test	P=0.223N	P=0.565N	P=0.276N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.290N	P=0.603	P=0.357N
Pancreatic Islets: Islet-Cell Adenoma			
Tumor Rates			
Overall *(b)*	0/47 (0%)	3/49 (6%)	1/49 (2%)
Adjusted *(c)*	0.0%	6.9%	2.3%
Terminal *(d)*	0/38 (0%)	2/42 (5%)	1/43 (2%)
Statistical Tests *(e)*			
Life Table	P=0.587	P=0.140	P=0.524
Incidental Tumor Test	P=0.538	P=0.101	P=0.524
Cochran-Armitage Trend, Fisher Exact Tests	P=0.566	P=0.129	P=0.510

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

	Control	Low Dose	High Dose
Mammary Gland: Adenoma or Fibroadenoma			
Tumor Rates			
Overall *(b)*	22/50 (44%)	10/49 (20%)	10/50 (20%)
Adjusted *(c)*	53.7%	22.6%	22.7%
Terminal *(d)*	19/38 (50%)	8/42 (19%)	9/43 (21%)
Statistical Tests *(e)*			
Life Table	P=0.007N	P=0.004N	P=0.003N
Incidental Tumor Test	P=0.011N	P=0.008N	P=0.006N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.014N	P=0.010N	P=0.009N
Clitoral Gland: Adenoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	2/49 (4%)	2/50 (4%)
Adjusted *(c)*	7.9%	4.8%	4.7%
Terminal *(d)*	3/38 (8%)	2/42 (5%)	2/43 (5%)
Statistical Tests *(e)*			
Life Table	P=0.410N	P=0.454N	P=0.444N
Incidental Tumor Test	P=0.410N	P=0.454N	P=0.444N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.457N	P=0.510N	P=0.500N
Clitoral Gland: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	2/49 (4%)	3/50 (6%)
Adjusted *(c)*	7.9%	4.8%	7.0%
Terminal *(d)*	3/38 (8%)	2/42 (5%)	3/43 (7%)
Statistical Tests *(e)*			
Life Table	P=0.601N	P=0.454N	P=0.605N
Incidental Tumor Test	P=0.601N	P=0.454N	P=0.605N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.578	P=0.510N	P=0.661
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(b)*	9/49 (18%)	5/47 (11%)	5/48 (10%)
Adjusted *(c)*	22.6%	12.2%	11.9%
Terminal *(d)*	7/37 (19%)	5/41 (12%)	5/42 (12%)
Statistical Tests *(e)*			
Life Table	P=0.147N	P=0.149N	P=0.139N
Incidental Tumor Test	P=0.164N	P=0.193N	P=0.167N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.204N	P=0.218N	P=0.205N
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(b)*	9/49 (18%)	6/47 (13%)	6/48 (13%)
Adjusted *(c)*	27.6%	14.6%	14.3%
Terminal *(d)*	7/37 (19%)	6/41 (15%)	6/42 (14%)
Statistical Tests *(e)*			
Life Table	P=0.218N	P=0.227N	P=0.214N
Incidental Tumor Test	P=0.239N	P=0.282N	P=0.249N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.296N	P=0.319N	P=0.303N

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

(a) Dosed groups received doses of 1,000 or 3,000 ppm of 2-biphenylamine hydrochloride in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at the end of the study.
(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 before the end of the study as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

PRECHRONIC STUDIES

Single-Dose Study

Male and female mice given a single dose of 10 g/kg technical-grade 2-biphenylamine died within 24 hours following administration. Prior to death, these animals showed hyperactivity, prostration, and shallow breathing. Necropsy showed dark intestinal contents, enlarged lymph nodes, and reddened nasal conchae. Macroscopic examination of animals in the remaining dose groups revealed the presence of enlarged Peyer's patches. In addition, mice receiving 0.01 or 0.1 g/kg doses had slight opacity in the lens region of the eye. Mice receiving the 1 g/kg dose had mesenteric lymph node enlargement. One mouse in this group died because of a gavage accident. There was a slight change in body weight of animals at the end of the 14-day observation period (Appendix L).

On the basis of this study, dose levels of 0, 1,000, 3,000, 10,000, and 30,000 ppm technical-grade 2-biphenylamine in feed were selected for use in the 14-day study.

Fourteen-Day Study with Technical-Grade 2-Biphenylamine

Survival and body weight changes in mice receiving feed containing various levels (0, 1,000, 3,000, 10,000, or 30,000 ppm) of technical-grade 2-biphenylamine are depicted in Table 12. All male and female mice survived the 14-day experimental period. Male mice given feed containing 1,000 or 3,000 ppm showed an increase in mean body weight, while those receiving 10,000 or 30,000 ppm exhibited a loss in weight. In female mice, loss in mean body weight was observed in the group of mice receiving 30,000 ppm. A dose-related depression in mean body weight was observed in female mice.

All dosed mice had enlarged lymph nodes and hemorrhage in the renal medulla. Thymic atrophy was observed in all mice receiving 30,000 ppm of technical-grade 2-biphenylamine. Splenomegaly was observed in all male and female mice receiving diets containing 3,000, 10,000, or 30,000 ppm. Mice dosed with 1,000 ppm did not exhibit splenomegaly (Table 13).

Dose levels of technical-grade 2-biphenylamine recommended for use in the 13-week study were 0, 300, 1,000 3,000, 10,000, and 30,000 ppm, based on survival and body weight changes of test animals in this study.

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING TECHNICAL-GRADE 2-BIPHENYLAMINE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Change Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Males					
0	9/9	20.7 ±0.47	24.0 ±0.47	+3.3 ±0.44	
1,000	5/5	20.6 ±0.81	22.2 ±0.86	+1.6 ±0.24	-51.5
3,000	5/5	19.8 ±0.37	23.2 ±0.73	+3.4 ±0.51	+ 3.0
10,000	5/5	20.2 ±0.66	18.6 ±1.21	-1.6 ±0.87	-148.5
30,000	5/5	20.2 ±0.37	18.0 ±0.55	-2.2 ±0.37	-166.7
Females					
0	8/8	18.0 ±0.33	19.4 ±0.68	+1.4 ±0.53	
1,000	5/5	17.2 ±0.37	18.2 ±0.20	+1.0 ±0.45	-28.6
3,000	5/5	17.0 ±0.45	17.6 ±0.60	+0.6 ±0.24	-57.1
10,000	5/5	16.8 ±0.80	17.0 ±0.89	+0.2 ±0.49	-85.7
30,000	5/5	16.8 ±0.58	14.8 ±0.37	-2.0 ±0.63	-242.9

(a) Number surviving/number in the group.
(b) Mean weight change of the group ± standard error of the mean.
(c) Weight change of the dosed group relative to that of the controls ▫

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

TABLE 13. INCIDENCE OF SPLENIC ENLARGEMENT IN MICE FED DIETS CONTAINING TECHNICAL-GRADE 2-BIPHENYLAMINE OR THE MOLAR EQUIVALENT OF 2-BIPHENYLAMINE HYDROCHLORIDE FOR 14 DAYS

Compound	Dose (ppm)	Males	Females
Technical-Grade 2-Biphenylamine	0	0/5	0/5
	1,000	0/5	0/5
	3,000	5/5	5/5
	10,000	5/5	5/5
	30,000	5/5	5/5
2-Biphenylamine Hydrochloride	0	0/5	0/5
	400	0/5	0/5
	1,200	0/5	0/5
	3,600	0/5	0/5
	12,100	0/5	1/5
	36,300	3/5	3/5

Fourteen-Day Study with 2-Biphenylamine Hydrochloride

Survival and body weight changes in mice dosed with 2-biphenylamine hydrochloride are depicted in Table 14. All experimental animals survived to the end of the 14-day study. Groups of male and female mice dosed with 12,100 or 36,300-ppm exhibited depression in mean body weight change relative to controls. The highest depression was observed at the 36,300-ppm dose level. It is evident from the data shown in Table 14 that there was no clear correlation between dose levels and the extent of body weight gain depression for doses of 12,100 ppm and lower.

The incidences of splenomegaly in mice fed diets containing various levels of 2-biphenylamine hydrochloride are shown in Table 13. The incidence was 3/5 in males dosed with 36,300 and 1/5 and 3/5 in females dosed with 12,000 and 36,300 ppm. The remaining groups of mice did not exhibit splenomegaly. The results shown in Table 13 indicate that the incidence of splenomegaly due to technical-grade 2-biphenylamine is greater than that due to 2-biphenylamine hydrochloride.

Thirteen-Week Study with Technical-Grade 2-Biphenylamine

Survival and mean body weight changes in mice consuming diets containing 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm of technical-grade 2-biphenylamine are summarized in Table 15. One female control mouse died on day 58. There were decreases in mean body weight gain relative to controls, with maximal changes of -42.4% and -50.5% in male and female mice fed 30,000 ppm technical-grade 2-biphenylamine. The hematologic data presented in Table 16 show a significant ($P < 0.001$) dose-related decrease in hemoglobin concentration and dose-related increases in leucocyte count in both male and female mice examined on week 1, 4, and 13. Hematocrit values showed significant ($P < 0.05$) dose-related decreases at week 1, but increases ($P < 0.001$) at week 13. Similarly, the red blood cell count showed marked ($P < 0.001$) decreases at weeks 1 and 4, but increases ($P < 0.01$) at week 13.

Necropsy of all animals revealed splenic enlargement in 10/10 males and 9/10 females dosed with 30,000 ppm. Histopathological examinations showed that nearly all mice dosed with 1,000 ppm or more exhibited hemosiderosis, congestion, and extramedullary hematopoiesis in their spleens. Erythroid hyperplasia in bone marrow was seen in 10/10 females and 9/10 males receiving 30,000 ppm and in 9/10 females and 7/10 males receiving 10,000 ppm. Transitional-cell hyperplasia was observed in bladders of 4/10 males and 4/10 females receiving 10,000 ppm and in 6/10 males and 10/10 females receiving 30,000 ppm (Table 17).

The results of the 14-day studies indicated that purified 2-biphenylamine hydrochloride was less toxic than technical-grade 2-biphenylamine; the weight gain depression and the incidence of splenic enlargement were less in animals administered the former compound (Tables 12, 13, and 14). These results also suggest that the histopathologic effects of 2-biphenylamine hydrochloride would be less severe than those seen in the 13-week study. For this reason, the Bioassay Program selected dose levels of 1,000 and 3,000 ppm of 2-biphenylamine hydrochloride for use in the chronic study.

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Change Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Males					
0	5/5	20.2 ± 0.80	23.0 ± 0.71	+2.8 ± 1.11	
400	5/5	20.2 ± 0.58	21.6 ± 0.51	+1.4 ± 0.68	-50.0
1,200	5/5	20.0 ± 0.71	23.8 ± 0.49	+3.8 ± 0.73	+35.7
3,600	5/5	20.0 ± 0.71	21.8 ± 0.37	+1.8 ± 0.37	-35.7
12,100	5/5	20.2 ± 0.80	22.6 ± 0.51	+2.4 ± 0.93	-14.3
36,300	5/5	20.2 ± 0.80	19.8 ± 0.49	-0.4 ± 0.81	-114.3
Females					
0	5/5	16.2 ± 0.37	18.2 ± 0.37	+2.0 ± 0.00	
400	5/5	16.2 ± 0.37	17.8 ± 0.20	+1.6 ± 0.24	-20.0
1,200	5/5	16.2 ± 0.37	18.4 ± 0.51	+2.2 ± 0.20	+10.0
3,600	5/5	16.2 ± 0.37	18.6 ± 0.24	+2.4 ± 0.24	+20.0
12,100	5/5	16.2 ± 0.37	18.0 ± 0.45	+1.8 ± 0.49	-10.0
36,300	5/5	16.2 ± 0.37	16.6 ± 0.40	+0.4 ± 0.24	-80.0

(a) Number surviving/number in the group.

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

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

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

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING TECHNICAL-GRADE 2-BIPHENYLAMINE FOR 13 WEEKS

Dose (ppm)	Survival *(a)* (Day of Death)	Mean Body Weight (grams)			Weight Change Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Males					
0	10/10	19.6 ± 0.34	33.5 ± 0.70	+13.9 ± 0.53	
300	10/10	19.6 ± 0.34	33.6 ± 1.18	+14.0 ± 1.26	+ 0.7
1,000	10/10	19.6 ± 0.34	35.1 ± 0.71	+15.5 ± 0.81	+11.5
3,000	10/10	19.6 ± 0.34	32.0 ± 1.13	+12.4 ± 1.08	-10.8
10,000	10/10	19.7 ± 0.37	32.1 ± 0.67	+12.4 ± 0.64	-10.8
30,000	10/10	19.6 ± 0.34	27.6 ± 0.62	+ 8.0 ± 0.56	-42.4
Females					
0	9/10 (58)	17.1 ± 0.26	26.6 ± 0.75	+ 9.5 ± 0.58	
300	10/10	17.0 ± 0.30	25.3 ± 0.78	+ 8.3 ± 0.60	-12.6
1,000	10/10	17.0 ± 0.30	24.9 ± 0.50	+ 7.9 ± 0.46	-16.8
3,000	10/10	17.0 ± 0.26	24.9 ± 0.75	+ 7.9 ± 0.59	-16.8
10,000	10/10	17.0 ± 0.26	24.8 ± 0.33	+ 7.8 ± 0.36	-17.9
30,000	10/10	17.0 ± 0.26	21.7 ± 0.30	+ 4.7 ± 0.33	-50.5

(a) Number surviving/number in the group. All calculations are based on those animals surviving to the end of the study.

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

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

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

TABLE 16. SUMMARY OF HEMATOLOGY DATA ON MICE FED DIETS CONTAINING TECHNICAL GRADE 2-BIPHENYLAMINE FOR 13 WEEKS *(a)*

Determination	Dose (ppm)	Weeks on Study: 1 — Males *(b)*	1 — Females *(c)*	4 — Males *(b)*	4 — Females *(c)*	13 — Males *(b)*	13 — Females *(c)*
Hemoglobin (g/100 ml)	0	15.6 ± 0.3	16.4 ± 0.2	15.6 ± 0.3	16.3 ± 0.4	14.9 ± 0.7	16.7 ± 0.3
	300	15.7 ± 0.3	16.1 ± 0.2	16.3 ± 0.4	15.9 ± 0.3	15.5 ± 0.2	15.8 ± 0.1 *(d)*
	1,000	15.0 ± 0.3	15.6 ± 0.2 *(d)*	15.4 ± 0.2	16.0 ± 0.5	15.4 ± 0.2	15.5 ± 0.2 *(d)*
	3,000	14.4 ± 0.4 *(d)*	15.1 ± 0.2 *(e)*	15.5 ± 0.2	16.6 ± 0.5	14.3 ± 0.9	15.1 ± 0.2 *(e)*
	10,000	13.1 ± 0.3 *(e)*	14.2 ± 0.4 *(e)*	14.4 ± 0.3 *(d)*	15.4 ± 0.4	14.7 ± 0.3	14.7 ± 0.4 *(e)*
	30,000	12.6 ± 0.3 *(e)*	13.6 ± 0.4 *(e)*	12.9 ± 0.3 *(e)*	15.2 ± 0.5 *(d)*	14.2 ± 0.3 *(d)*	14.8 ± 0.3 *(e)*
	Dose-Response	P<0.001	P<0.001	P<0.001	P<0.05	P<0.001	P<0.001
Hematocrit(%)	0	36.8 ± 0.8	38.6 ± 1.8	38.4 ± 1.5	40.8 ± 2.3	29.5 ± 1.7	40.0 ± 1.3
	300	36.7 ± 1.4	39.2 ± 0.9	42.7 ± 2.1	41.4 ± 1.6	45.1 ± 3.6 *(e)*	45.4 ± 1.1 *(d)*
	1,000	35.2 ± 1.0	37.0 ± 0.6	37.6 ± 1.0	39.2 ± 2.0	31.5 ± 3.7	60.9 ± 3.3 *(e)*
	3,000	33.7 ± 1.1	40.1 ± 1.4	40.5 ± 1.5	38.3 ± 1.0	29.0 ± 1.5	59.9 ± 2.5 *(e)*
	10,000	33.2 ± 1.4 *(d)*	30.4 ± 1.6 *(e)*	38.4 ± 1.2	41.2 ± 0.6	41.8 ± 3.1 *(e)*	49.5 ± 2.0 *(e)*
	30,000	34.3 ± 1.0	33.9 ± 1.0 *(d)*	36.8 ± 0.9	44.1 ± 1.1 *(d)*	48.3 ± 1.1 *(e)*	56.8 ± 2.4 *(e)*
	Dose-Response	P<0.05	P<0.01	NS	P<0.05	P<0.001	P<0.001
Red Blood Cell *(f)* (10^6/mm^3)	0	6.98 ± .11	7.00 ± .16	7.34 ± .19	7.68 ± .28	3.60 ± .24	5.34 ± .18
	300	6.99 ± .24	7.38 ± .09 *(d)*	7.74 ± .20	7.63 ± .21	5.99 ± .55 *(e)*	6.25 ± .16 *(e)*
	1,000	6.79 ± .18	7.15 ± .08	7.13 ± .16	7.30 ± .17	4.05 ± .55	7.64 ± .34 *(e)*
	3,000	6.50 ± .19	7.23 ± .20	7.53 ± .19	7.00 ± .12	3.71 ± .20	7.73 ± .20 *(e)*
	10,000	5.77 ± .16 *(e)*	5.33 ± .22 *(e)*	6.70 ± .22 *(d)*	6.86 ± .08 *(e)*	5.45 ± .40 *(e)*	6.51 ± .14 *(e)*
	30,000	5.33 ± .13 *(e)*	5.39 ± .10 *(e)*	5.43 ± .16 *(e)*	6.48 ± .12 *(e)*	6.08 ± .19 *(e)*	6.93 ± .11 *(e)*
	Dose-Response	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.01
Leucocytes (10^3/mm^3)	0	7.82 ± 0.49	9.45 ± 0.44	9.04 ± 0.60	6.87 ± 0.32	8.85 ± 0.76	7.06 ± 0.48
	300	7.76 ± 0.56	7.71 ± 0.49 *(e)*	9.84 ± 0.76	7.51 ± 0.35	5.73 ± 0.50 *(e)*	5.82 ± 0.35
	1,000	6.84 ± 0.54	8.26 ± 0.59	9.34 ± 1.03	8.48 ± 0.24 *(e)*	6.19 ± 1.11 *(d)*	6.27 ± 0.39
	3,000	7.35 ± 0.54	7.19 ± 0.45 *(e)*	10.86 ± 0.88	9.74 ± 0.84 *(e)*	9.30 ± 0.77	6.43 ± 0.29
	10,000	14.23 ± 0.92 *(e)*	15.50 ± 1.41 *(e)*	12.81 ± 2.71	12.10 ± 3.03 *(d)*	9.89 ± 0.77	8.16 ± 0.61
	30,000	36.58 ± 4.31 *(e)*	39.56 ± 7.32 *(e)*	25.74 ± 7.84 *(e)*	26.14 ± 7.92 *(e)*	13.80 ± 1.31 *(e)*	10.14 ± 0.62 *(e)*
	Dose-Response	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
Neutrophil/ Lymphocyte (%)	0	15/85	11/89	24/74	32/66	32/68	11/87
	300	13/85	8/92	47/51	33/66	25/73	55/43
	1,000	7/92	11/88	33/66	42/56	29/66	48/50
	3,000	13/85	14/84	42/58	44/55	32/67	46/54
	10,000	8/92	10/89	46/53	41/58	12/87	12/88
	30,000	12/87	7/91	38/60	44/55	11/88	9/90

(a) Values presented include the mean ± standard error.
(b) Values are based on orbital bleedings of 10 animals in each group at each time period.
(c) Values for each sample period are based on orbital bleedings of 10 animals in each group. Ten control animals were available for sampling at week 1, and 9 animals were available for sampling at weeks 4 and 13.
(d) $P < 0.05$ vs. controls.
(e) $P < 0.01$ vs. controls.
(f) For red blood cell determinations, two samples per animal were analyzed.

TABLE 17. INCIDENCE OF HISTOPATHOLOGIC EFFECTS IN MICE FED DIETS CONTAINING TECHNICAL-GRADE 2-BIPHENYLAMINE FOR 13 WEEKS

	Dose (ppm)											
	0		300		1,000		3,000		10,000		30,000	
Site and Effect:	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Spleen:												
Congestion	0/10	0/10	0/10	0/10	8/10	9/10	10/10	8/10	9/10	10/10	9/10	10/10
Thickened Capsule	0/10	0/10	0/10	0/10	0/10	0/10	1/10	1/10	4/10	0/10	6/10	3/10
Extramedullary Hematopoiesis	0/10	0/10	0/10	0/10	8/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Lymphoid Atrophy	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	5/10	4/10	8/10	3/10
Hemosiderosis	0/10	0/10	0/10	0/10	10/10	9/10	9/10	10/10	10/10	10/10	9/10	10/10
Liver:												
Pigment	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	10/10	10/10
Bone Marrow:												
Erythroid Hyperplasia	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	7/10	9/10	9/10	10/10
Peripheral Blood:												
Polychromasia	0/10	0/10	0/10	0/10	1/10	1/10	10/10	10/10	10/10	10/10	10/10	10/10
Anisocytosis	0/10	0/10	0/10	0/10	0/10	0/10	9/10	5/10	10/10	10/10	10/10	10/10
Poikilocytosis	0/10	0/10	0/10	0/10	0/10	0/10	1/10	0/10	10/10	9/10	10/10	9/10
Howell-Jolly Bodies	0/10	0/10	0/10	0/10	1/10	0/10	2/10	0/10	10/10	8/10	10/10	10/10
Target Cells	0/10	0/10	0/10	0/10	0/10	0/10	10/10	2/10	10/10	10/10	10/10	10/10
Urinary Bladder:												
Transitional-Cell Hyperplasia	0/10	0/10	0/10	0/10	0/10	0/10	1/10	0/10	4/10	4/10	6/10	10/10
Mucosal Thickening	0/10	0/10	1/10	1/10	0/10	2/10	3/10	2/10	4/10	3/10	4/10	0/10

CHRONIC STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

Body Weights and Food Consumption

At the end of 104 weeks, there was little difference in mean body weight changes of mice fed diets containing 2-biphenylamine and those of the controls (Figure 3 and Table 18).

Daily food consumption per mouse in low- and high-dose groups was 96% (7.4/7.7) and 101% (7.8/7.7) for males and 91% (7.8/8.6) and 95% (8.2/8.6) for females (Appendix M, Tables M3 and M4).

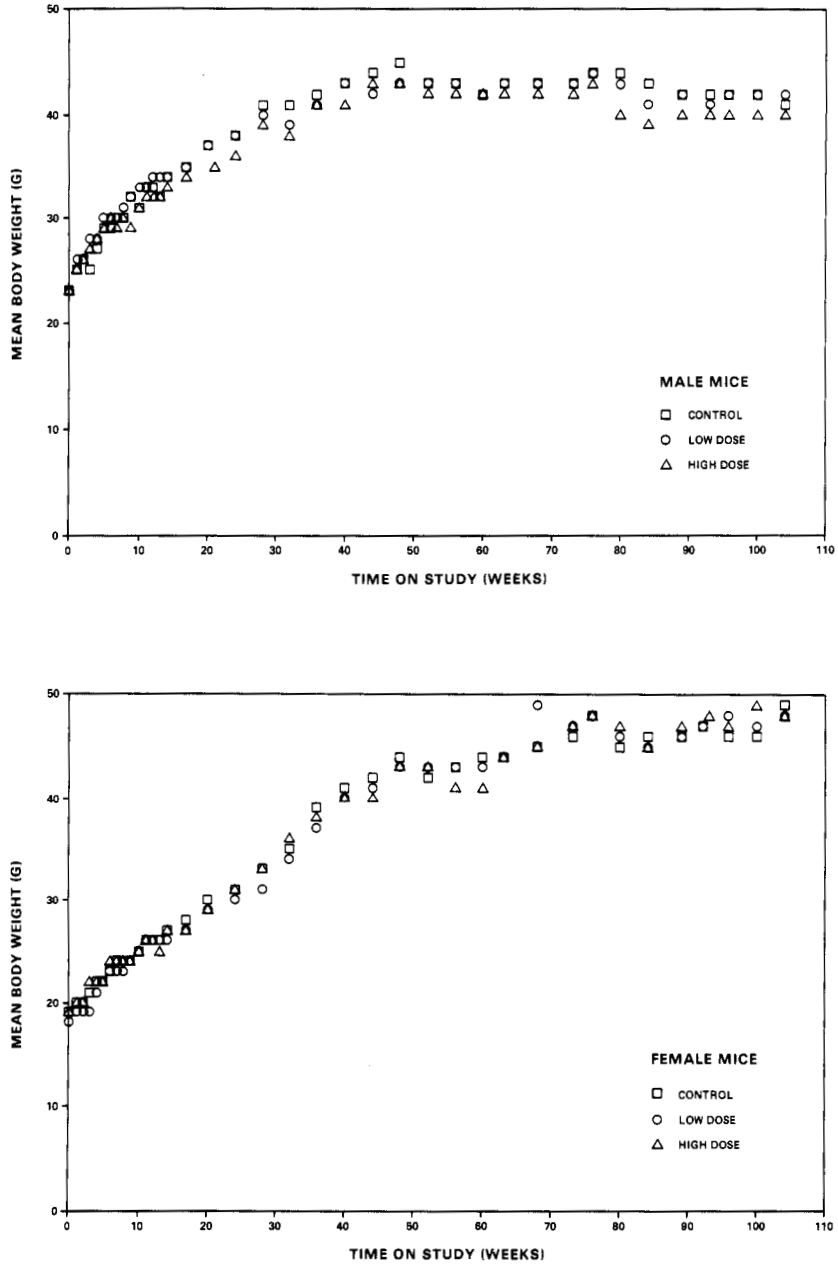

Figure 3. Growth Curves for Mice Fed Diets Containing 2-Biphenylamine Hydrochloride

TABLE 18. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF MICE FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE FOR 2 YEARS

		Cumulative Mean Body Weight Change (grams)			Weight Change Relative to Controls *(a)* (Percent)	
	Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males	0	23 *(b)*	23 *(b)*	23 *(b)*		
	4	4	5	5	+25	+25
	24	15	15	13	0	-13
	44	21	19	20	-10	- 5
	63	20	20	19	0	- 5
	84	20	18	16	-10	-20
	104	28	29	27	+ 4	- 4
	Final Body Weights	51	52	50	+ 2 *(c)*	- 2 *(c)*
Females	0	19 *(b)*	18 *(b)*	19 *(b)*		
	4	3	3	3	0	0
	24	12	12	12	0	0
	44	23	23	21	0	- 9
	63	25	26	25	+ 4	0
	84	27	27	26	0	- 4
	104	30	30	29	0	- 3
	Final Body Weights	49	48	48	- 2 *(c)*	- 2 *(c)*

(a) Weight change relative to controls =

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

(b) Initial weight

(c) Final body weight relative to controls (percent)

Clinical Signs and Survival

No untoward clinical signs related to administration were seen in experimental animals throughout the experimental period.

Probability estimates for survival depicted in Figure 4 show a significant reduction in survival rates of the high-dose male mice compared with the control and low-dose groups ($P < 0.001$ and $P=0.004$), respectively. There were no significant differences between the survival rates of the low-dose male mice and controls or between those of all female groups.

At the end of the 104-105-week period, the survival rates of male mice were 80%, 70%, and 42% for controls, low-dose, and high-dose mice, respectively. In the female mice, the survival rate for control females was compromised due to the accidental death of five animals at week 85 and the disappearance of one female mouse at week 84. The survival rates of female mice were 58%, 76%, and 56% for the controls, low-dose, and high-dose groups, respectively.

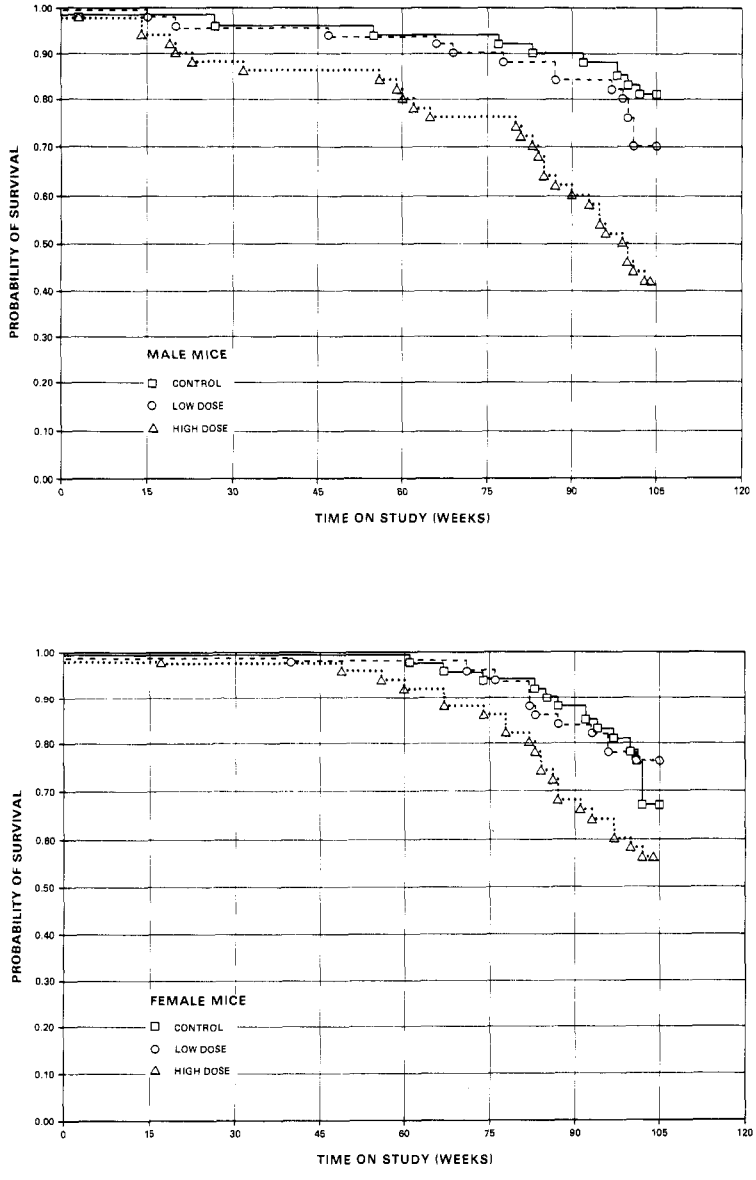

Figure 4. Survival Curves for Mice Fed Diets Containing 2-Biphenylamine Hydrochloride

Pathology and Statistical Analyses of Results

Histopathologic diagnoses of neoplasms occurring in mice are summarized in Appendix B, Tables B1 and B2. Tables B3 and B4 give the survival and tumor status for each individual animal in the male and female mouse studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Tables 20 and 21 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Circulatory System: Vascular neoplasms occurred at an increased incidence in dosed mice (Table 19). Hemangiosarcomas in the circulatory system were observed in a statistically significant positive relation to the administration of the compound in both male and female mice. These lesions were found in the circulatory system of the adipose tissue, liver, lymph nodes, spleen, and subcutaneous tissue. In males, the incidences were 0/50 for controls, 2/50 (4%) for the low-dose, and 3/50 (6%) for the high-dose group, with a significance level of P=0.040 as determined by a life table analysis trend test. In females, the incidences were 0/49 in the controls, 1/50 (2%) in the low-dose, and 7/50 (14%) in the high-dose group, and all trend statistics were significant ($P \leq 0.002$). The incidence in the high-dose group was significantly higher ($P < 0.010$) than that in the controls. [In this report, the terms hemangiosarcoma and angiosarcoma are used interchangeably; the former is preferred.]

The hemangiomas were small lesions with distended capillaries and anastomosing vascular cysts which were lined by fusiform endothelial cells. Cytoplasm of the cells was eosinophilic and nuclei were hyperchromatic. The hemangiosarcomas were characterized by cellular masses containing numerous blood filled spaces; these varied in size and in some tumors became cavernous with an occasional thrombus. Most of the neoplastic cells were elongated with variable-shaped nuclei containing evenly distributed chromatin. The eosinophilic cytoplasm varied in amount and at the periphery of the mass became quite elongated and filamentous, whereas cells near larger vascular spaces were more rounded. Mitotic figures were numerous. There were islands of necrosis in the large tumors.

Hematopoietic System: Lymph node lesions diagnosed as angiectasis were found in 2/49 control males, 7/47 low-dose males, 1/42 high-dose males, 2/47 low-dose females, and 1/47 high-dose females.

Lung: There was a significant ($P \leq 0.003$) dose-related decrease in alveolar/bronchial adenoma or carcinoma in male mice: controls, 16/50 (32%); low-dose, 6/50 (12%); high-dose 1/50 (2%). Both the low-dose and the high-dose male groups had significantly ($P < 0.05$) fewer tumors than the controls. The frequencies of lung tumors in female control and high-dose groups were similar (6/49, 1/50, 5/50), although the incidence in the low-dose group was slightly lower than those in the other two groups.

TABLE 19. NUMBER OF MICE WITH TUMORS OF THE CIRCULATORY SYSTEM IN THE 2-YEAR STUDY

	Males			Females		
	Control	Low-Dose	High-Dose	Control	Low-Dose	High-Dose
Number of Mice	50	50	50	49	50	50
Site and Morphology						
Subcutaneous Tissue						
Hemangioma	0	1	0	0	0	0
Hemangiosarcoma	0	0	0	0	0	3
Spleen						
Hemangioma	0	0	0	0	0	1
Hemangiosarcoma	0	1	0	0	0	1
Angiosarcoma	0	0	0	0	0	1
Lymph Node						
Hemangioma	0	1	0	0	0	0
Adipose Tissue						
Angiosarcoma	0	0	0	0	1	2
Liver						
Hemangioma	0	1	0	0	0	0
Angiosarcoma	0	2	3	0	0	1
Number of Mice with Hemangioma (all sites)	0	3	0	0	0	1
Number of Mice with Hemangiosarcomas (all sites)	0	2	3	0	1	7
Number of Mice with Hemangiomas or Hemangiosarcomas (all sites)	0	4	3	0	1	8

TABLE 20. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)*

	Control	Low Dose	High Dose
Subcutaneous Tissue: All Sarcomas			
Tumor Rates			
Overall *(b)*	4/50 (8%)	6/50 (12%)	4/50 (8%)
Adjusted *(c)*	9.2%	15.0%	14.1%
Terminal *(d)*	1/40 (3%)	2/35 (6%)	1/21 (5%)
Statistical Tests *(e)*			
Life Table	P=0.324	P=0.323	P=0.370
Incidental Tumor Test	P=0.183N	P=0.657	P=0.299N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.470N	P=0.370	P=0.643
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	14/50 (28%)	5/50 (10%)	1/50 (2%)
Adjusted *(c)*	35.0%	14.3%	4.8%
Terminal *(d)*	14/40 (35%)	5/35 (14%)	1/21 (5%)
Statistical Tests *(e)*			
Life Table	P=0.006N	P=0.037N	P=0.011N
Incidental Tumor Test	P=0.006N	P=0.037N	P=0.011N
Cochran-Armitage Trend, Fisher Exact Tests	P<0.001N	P=0.020N	P<0.001N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	16/50 (32%)	6/50 (12%)	1/50 (2%)
Adjusted *(c)*	40.0%	17.1%	4.8%
Terminal *(d)*	16/40 (40%)	6/35 (17%)	1/21 (5%)
Statistical Tests *(e)*			
Life Table	P=0.003N	P=0.028N	P=0.005N
Incidental Tumor Test	P=0.003N	P=0.028N	P=0.005N
Cochran-Armitage Trend, Fisher Exact Tests	P<0.001N	P=0.014N	P<0.001N
Hematopoietic System: Lymphoma			
Tumor Rates			
Overall *(b)*	6/50 (12%)	8/50 (16%)	7/50 (14%)
Adjusted *(c)*	13.8%	21.2%	26.2%
Terminal *(d)*	4/40 (10%)	6/35 (17%)	3/21 (14%)
Statistical Tests *(e)*			
Life Table	P=0.135	P=0.313	P=0.172
Incidental Tumor Test	P=0.517	P=0.402	P=0.600
Cochran-Armitage Trend, Fisher Exact Tests	P=0.500	P=0.387	P=0.500
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted *(c)*	0.0%	5.1%	11.7%
Terminal *(d)*	0/40 (0%)	1/35 (3%)	2/21 (10%)
Statistical Tests *(e)*			
Life Table	P=0.040	P=0.223	P=0.053
Incidental Tumor Test	P=0.119	P=0.183	P=0.087
Cochran-Armitage Trend, Fisher Exact Tests	P=0.113	P=0.247	P=0.121

TABLE 20. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Circulatory System: Hemangioma or Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	0/50 (0%)	4/50 (8%)	3/50 (6%)
Adjusted *(c)*	0.0%	10.3%	11.7%
Terminal *(d)*	0/40 (0%)	2/35 (6%)	2/21 (10%)
Statistical Tests *(e)*			
Life Table	P=0.071	P=0.055	P=0.053
Incidental Tumor Test	P=0.227	P=0.065	P=0.087
Cochran-Armitage Trend, Fisher Exact Tests	P=0.205	P=0.059	P=0.121
Liver: Adenoma			
Tumor Rates			
Overall *(b)*	5/50 (10%)	7/50 (14%)	1/50 (2%)
Adjusted *(c)*	12.5%	19.3%	3.7%
Terminal *(d)*	5/40 (13%)	6/35 (17%)	0/21 (0%)
Statistical Tests *(e)*			
Life Table	P=0.272N	P=0.292	P=0.296N
Incidental Tumor Test	P=0.166N	P=0.339	P=0.192N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.071N	P=0.380	P=0.102N
Liver: Carcinoma			
Tumor Rates			
Overall *(b)*	9/50 (18%)	12/50 (24%)	10/50 (20%)
Adjusted *(c)*	21.3%	29.1%	31.2%
Terminal *(d)*	7/40 (18%)	7/35 (20%)	3/21 (14%)
Statistical Tests *(e)*			
Life Table	P=0.110	P=0.236	P=0.126
Incidental Tumor Test	P=0.437N	P=0.296	P=0.601N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.521	P=0.312	P=0.500
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	14/50 (28%)	19/50 (38%)	11/50 (22%)
Adjusted *(c)*	33.2%	45.8%	33.7%
Terminal *(d)*	12/40 (30%)	13/35 (37%)	3/21 (14%)
Statistical Tests *(e)*			
Life Table	P=0.273	P=0.120	P=0.294
Incidental Tumor Test	P=0.187N	P=0.168	P=0.304N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.208N	P=0.198	P=0.322N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	1/49 (2%)	3/49 (6%)	1/48 (2%)
Adjusted *(c)*	2.3%	8.2%	3.2%
Terminal *(d)*	0/40 (0%)	2/35 (6%)	0/21 (0%)
Statistical Tests *(e)*			
Life Table	P=0.550	P=0.274	P=0.663
Incidental Tumor Test	P=0.392N	P=0.429	P=0.482N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.557N	P=0.309	P=0.747

TABLE 20. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Adrenal: Adenoma			
Tumor Rates			
Overall *(b)*	3/49 (6%)	2/49 (4%)	2/48 (4%)
Adjusted *(c)*	7.5%	5.7%	8.4%
Terminal *(d)*	3/40 (7%)	2/35 (6%)	1/21 (5%)
Statistical Tests *(e)*			
Life Table	P=0.471	P=0.561N	P=0.598
Incidental Tumor Test	P=0.621	P=0.561N	P=0.643N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.469N	P=0.500N	P=0.510N

(a) Dosed groups received doses of 1,000 or 3,000 ppm of 2-biphenylamine hydrochloride in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site (percent).
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at the end of the study (percent).
(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 before the end of the study as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

TABLE 21. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)*

	Control	Low Dose	High Dose
Subcutaneous Tissue: Sarcoma			
Tumor Rates			
Overall *(b)*	5/49 (10%)	1/50 (2%)	2/50 (4%)
Adjusted *(c)*	15.1%	2.6%	6.5%
Terminal *(d)*	2/29 (7%)	1/38 (3%)	1/28 (4%)
Statistical Tests *(e)*			
Life Table	P=0.261N	P=0.067N	P=0.260N
Incidental Tumor Test	P=0.312N	P=0.142N	P=0.334N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.213N	P=0.098N	P=0.210N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	6/49 (12%)	1/50 (2%)	4/50 (8%)
Adjusted *(c)*	17.1%	2.6%	12.3%
Terminal *(d)*	3/29 (10%)	1/38 (3%)	2/28 (7%)
Statistical Tests *(e)*			
Life Table	P=0.496N	P=0.037N	P=0.419N
Incidental Tumor Test	P=0.451N	P=0.074N	P=0.404N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.424N	P=0.053N	P=0.357N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	6/49 (12%)	1/50 (2%)	5/50 (10%)
Adjusted *(c)*	17.1%	2.6%	14.7%
Terminal *(d)*	3/29 (10%)	1/38 (3%)	2/28 (7%)
Statistical Tests *(e)*			
Life Table	P=0.531	P=0.037N	P=0.549N
Incidental Tumor Test	P=0.577	P=0.074N	P=0.541N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.584N	P=0.053N	P=0.486N
Hematopoietic System: Lymphoma			
Tumor Rates			
Overall *(b)*	10/49 (20%)	17/50 (34%)	9/50 (18%)
Adjusted *(c)*	29.1%	36.4%	26.3%
Terminal *(d)*	6/29 (21%)	9/38 (24%)	5/28 (18%)
Statistical Tests *(e)*			
Life Table	P=0.444N	P=0.232	P=0.562N
Incidental Tumor Test	P=0.380N	P=0.040	P=0.573N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.305N	P=0.098	P=0.480N
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	0/49 (0%)	1/50 (2%)	7/50 (14%)
Adjusted *(c)*	0.0%	2.6%	23.4%
Terminal *(d)*	0/29 (0%)	1/38 (3%)	6/28 (21%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.554	P=0.008
Incidental Tumor Test	P<0.001	P=0.554	P=0.008
Cochran-Armitage Trend, Fisher Exact Tests	P=0.002	P=0.505	P=0.007

TABLE 21. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Circulatory System: Hemangioma or Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	0/49 (0%)	1/50 (2%)	8/50 (16%)
Adjusted *(c)*	0.0%	2.6%	26.9%
Terminal *(d)*	0/29 (0%)	1/38 (3%)	7/28 (25%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.554	P=0.004
Incidental Tumor Test	P<0.001	P=0.554	P=0.004
Cochran-Armitage Trend, Fisher Exact Tests	P=0.001	P=0.505	P=0.003
Liver: Adenoma			
Tumor Rates			
Overall *(b)*	3/49 (6%)	5/50 (10%)	4/50 (8%)
Adjusted *(c)*	10.3%	13.2%	14.3%
Terminal *(d)*	3/29 (10%)	5/38 (13%)	4/28 (14%)
Statistical Tests *(e)*			
Life Table	P=0.439	P=0.511	P=0.481
Incidental Tumor Test	P=0.439	P=0.511	P=0.481
Cochran-Armitage Trend, Fisher Exact Tests	P=0.510	P=0.369	P=0.511
Liver: Carcinoma			
Tumor Rates			
Overall *(b)*	4/49 (8%)	4/50 (8%)	6/50 (12%)
Adjusted *(c)*	11.7%	10.0%	19.5%
Terminal *(d)*	2/29 (7%)	3/38 (8%)	4/28 (14%)
Statistical Tests *(e)*			
Life Table	P=0.234	P=0.543N	P=0.329
Incidental Tumor Test	P=0.230	P=0.613	P=0.288
Cochran-Armitage Trend, Fisher Exact Tests	P=0.310	P=0.631N	P=0.383
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	7/49 (14%)	9/50 (18%)	10/50 (20%)
Adjusted *(c)*	21.5%	22.8%	32.9%
Terminal *(d)*	5/29 (17%)	8/38 (21%)	8/28 (29%)
Statistical Tests *(e)*			
Life Table	P=0.195	P=0.583	P=0.255
Incidental Tumor Test	P=0.193	P=0.483	P=0.225
Cochran-Armitage Trend, Fisher Exact Tests	P=0.296	P=0.410	P=0.314
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	9/43 (21%)	8/42 (19%)	6/41 (15%)
Adjusted *(c)*	33.3%	22.2%	25.0%
Terminal *(d)*	9/27 (33%)	8/36 (22%)	6/24 (25%)
Statistical Tests *(e)*			
Life Table	P=0.374N	P=0.245N	P=0.367N
Incidental Tumor Test	P=0.374N	P=0.245N	P=0.367N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.282N	P=0.522N	P=0.321N

TABLE 21. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

(a) Dosed groups received doses of 1,000 or 3,000 ppm of 2-biphenylamine hydrochloride in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at the end of the study.
(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 before the end of the study as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

A set of preliminary studies (a single-dose study, a 14-day study, and a 13-week study) was conducted with technical-grade 2-biphenylamine. Because the technical-grade 2-biphenylamine was found to contain 2.5% 4-biphenylamine, a known carcinogen, a decision was made to reduce the level of the contaminant from the material to be used in the chronic test. The best available method was based on conversion of recrystallized 2-biphenylamine to 2-biphenylamine hydrochloride. A new 14-day study was performed with 2-biphenylamine hydrochloride. The batch of 2-biphenylamine hydrochloride used for the 14-day study contained 0.198% 4-biphenylamine hydrochloride. The four batches of 2-biphenylamine hydrochloride used in the chronic study contained 0.006% to 0.049% 4-biphenylamine.

Results of the 14-day studies in rats indicated that technical-grade 2-biphenylamine was more toxic than purified 2-biphenylamine hydrochloride, as evidenced by greater weight gain depression (Tables 2 and 4) and a greater incidence of splenic enlargement (Table 3). Inferring that the histopathologic and hematologic effects of 2-biphenylamine hydrochloride would be less severe than those seen in the 13-week study of the free amine, the Bioassay Program set doses of 1,000 and 3,000 ppm of the hydrochloride salt for the chronic study.

In the 14-day and 13-week studies, splenomegaly was observed in male and female rats (10,000 ppm and 30,000 ppm for the amine; 36,300 ppm for the salt) and mice (3,000-30,000 ppm for the amine; 36,300 ppm for the salt) fed diets containing technical-grade 2-biphenylamine or its hydrochloride salt (Table 3 for rats and Table 13 for mice). Increased extramedullary hematopoiesis in this organ may have been responsible for the splenomegaly. Destruction of erythrocytes and the resulting anemia are factors known to stimulate erythropoiesis. Evidence for these conditions is indicated by the compound-related and dose-dependent decreases in hematocrit values of hemoglobin concentration and in red blood cell counts in rats and mice fed the various dose levels of 2-biphenylamine (Table 6 for rats and Table 16 for mice). Moreover, aromatic amines structurally related to 2-biphenylamine induce methemoglobinemia leading to Heinz body formation and eventual destruction of erythrocytes (Kiese, 1967; Smith, 1980).

Polycystic kidney was observed in all male and female rats receiving 30,000 ppm technical-grade 2-biphenylamine for 13 weeks (Table 7). This pathologic condition is similar to that observed in kidneys of rats receiving the structurally related chemical, diphenylamine (Thomas *et al.*, 1967).

Survival of rats in the chronic study was not affected by administration of 2-biphenylamine hydrochloride. After week 22, mean body weight changes of high-dose rats were slightly lower than those of controls, ranging from 4% to 13% below the mean body weight changes of the controls. Inflammatory cells and interstitial fibrosis were found at increased incidences in the kidneys of dosed male rats as compared with controls and were considered to be an effect related to administration. Although polycystic kidney and splenomegaly were observed in the prechronic studies, these changes were not encountered in the NCI/NTP chronic studies.

Leukemia in male rats and mammary fibroadenomas in female rats occurred at significantly lower incidences in dosed rats when compared with concurrent controls. Incidences of male rats with leukemia were 15/50 (30%), 1/50 (2%), and 4/50 (8%) for controls, low-, and high-dose groups, respectively. The historical incidence of control F344/N male rats with leukemia at this laboratory is 195/1,016 (19.2%), with group incidences ranging from 0/50 (0%) to 23/50 (46%). Incidences of female rats with fibroadenomas of the mammary gland were 22/50 (44%), 10/49 (20%), and 9/50 (20%) for controls, low-, and high-dose groups, respectively. The historical incidence of female F344/N rats with these tumors at this laboratory is 294/1,071 (27.5%), with a range of 10%-46%. In both of these instances the concurrent control rates were well above the historical control incidences for F344/N rats at this laboratory, although the decrease in the incidence of leukemia remains significant ($P < 0.05$) when compared with historical controls.

The absence of an observed carcinogenic response by F344/N rats exposed to 2-biphenylamine may be due to their lack of ability to form the N-hydroxy derivative (Gorrod and Carey, 1970). 4-Biphenylamine is N-hydroxylated and has been demonstrated to cause cancer in multiple species (Althouse *et al.*, 1980).

Survival of high-dose female mice in the chronic study was not significantly less than that of the controls. Survival of high-dose male mice was significantly ($P < 0.01$) less than that of low-dose male and control mice. After week 22, mean body weights of high-dose male mice were slightly lower than those of the controls.

IV. DISCUSSION AND CONCLUSIONS

Administration of 2-biphenylamine hydrochloride significantly ($P \leq 0.002$) increased the incidence of hemangiosarcoma in female mice; the incidence in the high-dose group was significantly higher ($P < 0.010$) than that in the controls. The incidence of this tumor in high-dose female mice (7/50,14%) was greater than the historical incidence in control female B6C3F1 mice at this laboratory: 6/816 (0.7%), with group incidences ranging from 0/50 (0%) to 3/50 (6%). The increased incidence of hemangiosarcomas in high-dose female mice is considered to have been caused by administration of 2-biphenylamine hydrochloride. The conclusion that this was due to 2-biphenylamine rather than the contaminant, 4-biphenylamine, is supported by the absence of urinary bladder tumors, which are peculiar to 4-biphenylamine.

Hemangiosarcomas occurred in male mice with a significant positive trend (P=0.040 by a life table test). The increased incidence of hemangiosarcomas in the high-dose group (3/50, 6%) was not significant (P=0.053) in individual comparisons with the incidence in the control group, but development of hemangiosarcomas in high-dose male mice may have been curtailed by the significantly shortened survival in this group. The historical incidence of this tumor in control male B6C3F1 mice at this laboratory is 7/803 (0.9%), with group incidences ranging from 0/50 (0%) to 2/50 (4%). Although the evidence is strongly suggestive for associating hemangiosarcomas in male mice with administration of 2-biphenylamine hydrochloride, this chemical is not regarded as being unequivocally carcinogenic in male mice because of the relatively low incidence in the high-dose group.

Hemangiosarcomas have been observed at statistically significant increased incidences in B6C3F1 mice administered other nitrogen-containing aromatic compounds in NCI/NTP carcinogenesis bioassays (NCI, 1978a, 1978b, 1979, and Table 22). Hemangiosarcomas were

TABLE 22. INCIDENCE OF HEMANGIOSARCOMAS (OR ANGIOSARCOMAS) IN MICE FED DIETS CONTAINING VARIOUS AROMATIC AMINES AND NITRO COMPOUNDS

Compound	Strain of Mouse	Dose, Duration	Incidence				Reference
			Males		Females		
			Control	High Dose	Control	High Dose	
2-Biphenylamine hydrochloride	B6C3F1	3,000 ppm for 103 weeks	0/50	3/50	0/49	7/50	Present Study
Nitrofen	B6C3F1	4,696 ppm for 78 weeks	0/20 0/74 *(a)*	4/48	1/18 2/80 *(a)*	5/44	NCI, 1978b
Michler's Ketone	B6C3F1	1,250 ppm for 78 weeks	0/19	20/50	2/19	2/50	NCI, 1979
4,4'-Methylene-bis (2-chloroaniline)	CD-1	2,000 ppm for 18 months, then 6 months observation	0/18	3/20	0/20	2/14	Russfield *et al.*, 1975
2-Methyl-1-nitroanthraquinone	B6C3F1	300 ppm for 37-39 weeks	1/49	42/43	0/48	35/38	NCI, 1978a; Murthy *et al.*, 1977

(a) Pooled control.

observed in 20/50 male mice fed diets containing 1,250 ppm Michler's ketone—4,4'-bis(dimethylamino)benzophenone—for 78 weeks, compared with 0/19 in the controls and 2/50 in females receiving the same dose (NCI, 1979). The tumor was also found in 42/43 males and 35/38 females fed diets containing 300 ppm 2-methyl-1-nitroanthraquinone for 37-39 weeks (NCI, 1978a) and in 4/48 males receiving diets containing 4,696 ppm nitrofen (2,4-dichlorophenyl-p-nitrophenyl ether) for 78 weeks (NCI, 1978b). Hemangiosarcomas were observed in 3/20 CD-1 mice fed diets containing 2,000 ppm of 4,4'-methylene-bis(2-chloroaniline), compared with 0/18 in the controls (Russfield *et al.*, 1975). Further studies would be needed to determine if a common mechanism is involved in the induction of hemangiosarcomas by these compounds.

Lung tumors (the combined incidence of adenomas and carcinomas) occurred in male mice with a significant ($P \leq 0.003$) negative trend. Control incidences were 16/50 (32%) compared with 6/50 (12%) for low-dose and 1/50 (2%) for the high-dose group. The historical incidence of control male B6C3F1 mice with these tumors at this laboratory is 173/798 (21.6%).

Oral administration of the structurally related 4-biphenylamine (1.5 mg/week) for 52 weeks was associated with an increased incidence of hepatomas in male C57 x IF mice (Clayson *et al.*, 1967). Bladder tumors were found in 2/12 mice that received 4-biphenylamine (1 mg/week) for 38 weeks, followed by 62 weeks of observation (Clayson *et al.*, 1965). However, in the current study mice of both sexes fed either low-dose or high-dose diets containing purified 2-biphenylamine hydrochloride with 0.006%-0.049% 4-biphenylamine for 103 weeks did not develop bladder cancer. This suggests that 4-biphenylamine at the level found contaminating this sample may not be sufficient to produce this tumor in mice. In this study, the weekly consumption of 4-biphenylamine at its highest level of contamination (0.049%) was 23.8 and 75.6 μg/animal in the low-dose and high-dose male mice, respectively, and 25.2 and 79 μg in the corresponding dosed groups of female mice. These consumption values were approximately 41-fold lower for the low-dose mice and 13-fold lower for the high-dose mice than the weekly amount used by Clayson *et al.*, (1965) in their 38-week study in mice.

Literature searches did not generate any information regarding an association between the exposure to 4-biphenylamine and an increased incidence of hemangiosarcoma in any animal species.

Conclusions: Under the conditions of this bioassay, 2-biphenylamine hydrochloride was not carcinogenic for F344/N rats of either sex. 2-Biphenylamine hydrochloride was carcinogenic for B6C3F1 female mice, inducing hemangiosarcomas at various sites. The evidence for an association between the administration of 2-biphenylamine hydrochloride and the increased incidence of hemangiosarcomas in male mice was equivocal.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)	2 (4%)	1 (2%)
BASAL-CELL CARCINOMA			1 (2%)
SEBACEOUS ADENOCARCINOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
CARCINOMA,NOS		1 (2%)	
SQUAMOUS CELL CARCINOMA			1 (2%)
FIBROMA	6 (12%)	2 (4%)	4 (8%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
CARCINOMA, NOS, METASTATIC		1 (2%)	
CARCINOMA, NOS, UNC PRIM OR META	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	4 (8%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA,NOS	1 (2%)		
MYELOMONOCYTIC LEUKEMIA	14 (28%)	1 (2%)	4 (8%)
#SPLEEN	(48)	(50)	(50)
SARCOMA, NOS		1 (2%)	
#LYMPH NODE	(48)	(49)	(48)
MESOTHELIOMA, METASTATIC		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*EPIDIDYMIS	(50)	(50)	(50)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
CARCINOMA, NOS, METASTATIC		1 (2%)	
#PANCREATIC DUCT	(48)	(50)	(47)
ADENOMA, NOS	1 (2%)		
#STOMACH	(47)	(50)	(49)
SQUAMOUS CELL CARCINOMA	1 (2%)		
#JEJUNUM	(47)	(49)	(46)
ADENOCARCINOMA, NOS	1 (2%)		
#COLON	(42)	(48)	(47)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
CARCINOMA, NOS, UNC PRIM OR META	1 (2%)		
TUBULAR-CELL ADENOMA		1 (2%)	1 (2%)
#URINARY BLADDER	(48)	(50)	(47)
TRANSITIONAL-CELL PAPILLOMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(45)	(48)
ADENOMA, NOS	16 (36%)	17 (38%)	13 (27%)
CRANIOPHARYNGIOMA			1 (2%)
#ADRENAL	(48)	(50)	(49)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA	12 (25%)	12 (24%)	8 (16%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(47)	(49)	(46)
FOLLICULAR-CELL ADENOMA			1 (2%)
C-CELL ADENOMA	2 (4%)	7 (14%)	1 (2%)
C-CELL CARCINOMA	1 (2%)		1 (2%)
#PARATHYROID	(25)	(28)	(28)
ADENOMA, NOS		1 (4%)	1 (4%)
#PANCREATIC ISLETS	(48)	(50)	(47)
ISLET-CELL ADENOMA	4 (8%)	4 (8%)	4 (9%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS			1 (2%)
FIBROADENOMA	4 (8%)		1 (2%)
*PENIS	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS			1 (2%)
SQUAMOUS CELL PAPILLOMA			1 (2%)
ADENOMA, NOS	8 (16%)	4 (8%)	4 (8%)
#TESTIS	(49)	(50)	(49)
INTERSTITIAL-CELL TUMOR	47 (96%)	50 (100%)	45 (92%)
MESOTHELIOMA, NOS			1 (2%)
*SCROTUM	(50)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(50)
CARCINOMA,NOS		1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(50)	(50)
OSTEOMA			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SARCOMA, NOS, METASTATIC		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	11	7	7
MORIBUND SACRIFICE	3	1	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	42	40
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	49	50	47
TOTAL PRIMARY TUMORS	127	113	102
TOTAL ANIMALS WITH BENIGN TUMORS	49	50	47
TOTAL BENIGN TUMORS	106	104	90
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	9	8
TOTAL MALIGNANT TUMORS	19	9	9
TOTAL ANIMALS WITH SECONDARY TUMORS#		5	
TOTAL SECONDARY TUMORS		5	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			2
TOTAL UNCERTAIN TUMORS			3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC	2		
TOTAL UNCERTAIN TUMORS	2		

@ INCLUDES AUTOLYZED ANIMALS
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		1 (2%)
SARCOMA, NOS			1 (2%)
*SUBCUT TISSUE	(50)	(49)	(50)
SARCOMA, NOS			2 (4%)
FIBROMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
NEOPLASM, NOS			1 (2%)
SQUAMOUS CELL CARCINOMA			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
LEUKEMIA,NOS	1 (2%)		
MYELOMONOCYTIC LEUKEMIA	4 (8%)	1 (2%)	2 (4%)
*HEMATOPOIETIC SYSTEM	(50)	(49)	(50)
NEOPLASM, NOS	1 (2%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
NEOPLASTIC NODULE	1 (2%)	5 (10%)	1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREAS	(47)	(49)	(49)
ACINAR-CELL ADENOMA	1 (2%)		
URINARY SYSTEM			
#URINARY BLADDER	(49)	(48)	(50)
TRANSITIONAL-CELL PAPILLOMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(48)	(50)
ADENOMA, NOS	33 (70%)	38 (79%)	38 (76%)
#ADRENAL	(50)	(49)	(50)
CORTICAL ADENOMA			2 (4%)
PHEOCHROMOCYTOMA	2 (4%)		3 (6%)
#THYROID	(49)	(47)	(49)
FOLLICULAR-CELL ADENOMA	1 (2%)		
C-CELL ADENOMA	2 (4%)	4 (9%)	1 (2%)
C-CELL CARCINOMA	3 (6%)	1 (2%)	2 (4%)
#PANCREATIC ISLETS	(47)	(49)	(49)
ISLET-CELL ADENOMA		3 (6%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS	1 (2%)		
FIBROADENOMA	22 (44%)	10 (20%)	9 (18%)
*CLITORAL GLAND	(50)	(49)	(50)
CARCINOMA,NOS			1 (2%)
ADENOMA, NOS	3 (6%)	2 (4%)	2 (4%)
#UTERUS	(49)	(47)	(48)
ADENOCARCINOMA, NOS		1 (2%)	
CYSTADENOMA, NOS		1 (2%)	
SARCOMA, NOS	1 (2%)	1 (2%)	
ENDOMETRIAL STROMAL POLYP	9 (18%)	5 (11%)	5 (10%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOMETRIAL STROMAL SARCOMA		1 (2%)	1 (2%)
#OVARY	(49)	(48)	(49)
THECOMA		1 (2%)	
GRANULOSA-CELL TUMOR	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(49)	(50)
ASTROCYTOMA			1 (2%)
SPECIAL^SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*THORAX	(50)	(49)	(50)
ADENOCA/SQUAMOUS METAPLASIA, MET			1 (2%)
*PELVIC ORGANS	(50)	(49)	(50)
SARCOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
SITE UNKNOWN			
CARCINOMA,NOS	1		
ADENOCA/SQUAMOUS METAPLASIA			1

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	10	4	4
MORIBUND SACRIFICE	2	3	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	38	42	43
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS	*		
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	46	45	46
TOTAL PRIMARY TUMORS	92	77	79
TOTAL ANIMALS WITH BENIGN TUMORS	43	43	43
TOTAL BENIGN TUMORS	77	65	63
TOTAL ANIMALS WITH MALIGNANT TUMORS	10	6	12
TOTAL MALIGNANT TUMORS	12	6	14
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	6	2
TOTAL UNCERTAIN TUMORS	3	6	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

CONTROL

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	085	105	105	080	078	094	105	105	094	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN SQUAMOUS CELL PAPILLOMA	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
														X											
SUBCUTANEOUS TISSUE FIBROMA	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
				X		X	X	X										X							
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI CARCINOMA, NOS, UNC PRIM OR META ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
							X																		
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	-	-	+	+	+	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS ADENOMA, NOS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
							X																		
ESOPHAGUS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
STOMACH SQUAMOUS CELL CARCINOMA	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+
														X											
SMALL INTESTINE ADENOCARCINOMA, NOS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+
URINARY SYSTEM																									
KIDNEY CARCINOMA, NOS, UNC PRIM OR META	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
URINARY BLADDER TRANSITIONAL-CELL PAPILLOMA	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
									X																
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	+ X	+	-	-	+	+	+	+	+ X	+	+	+ X	+ X	+ X	-	+	+	+ X	+	+ X	+ X	+ X	+	+ X
ADRENAL PHEOCHROMOCYTOMA	+	+	+	+	-	+ X	+ X	+	+	+ X	+	+ X	+	+	+	-	+ X	+	+	+ X	+	+	+	+	+
THYROID C-CELL ADENOMA C-CELL CARCINOMA	+	+	+	+	-	+	+ X	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+ X	+	+	+
PARATHYROID	+	+	-	+	-	+	+	+	+	+	-	-	-	-	+	-	-	+	-	-	+	-	-	+	-
PANCREATIC ISLETS ISLET-CELL ADENOMA	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+ X	+ X	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND FIBROADENOMA	N	N	+ X	N	N	+	+	N	N	N	N	N	N	+	N	N	N	+	N	N	N	N	+ X	+ X	N	N
TESTIS INTERSTITIAL-CELL TUMOR	+ X	+ X	+ X	+	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X
PROSTATE	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+
PENIS SQUAMOUS CELL PAPILLOMA	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PREPUTIAL/CLITORAL GLAND ADENOMA, NOS	N X	N	N	N	N	N	N	N X	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N
EPIDIDYMIS HEMANGIOMA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND SQUAMOUS CELL CARCINOMA	N	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS LEUKEMIA,NOS MYELOMONOCYTIC LEUKEMIA	N	N	N X	N	N	N X	N	N X	N X	N X	N	N	N	N	N X	N	N	N	N	N X	N	N	N	N	N

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

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

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

ANIMAL NUMBER	0262	0267	0268	0269	0330	0311	0312	0333	0334	0335	0336	0337	0338	0339	0340	0341	0342	0343	0344	0345	0346	0347	0348	0349	0350	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	094	100	095	104	105	105	103	105	091	100	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	50*
FIBROMA																	X									6
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, UNC PRIM OR META																										1
ALVEOLAR/BRONCHIOLAR ADENOMA		X								X																2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYMUS	+	+	+	+	-	-	+	-	-	-	-	+	+	+	+	-	-	+	+	+	+	+	+	+	-	37
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOMA, NOS																										1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SQUAMOUS CELL CARCINOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOCARCINOMA, NOS															X											1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	-	-	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA, NOS, UNC PRIM OR META										X																1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
TRANSITIONAL-CELL PAPILLOMA																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	45
ADENOMA, NOS		X									X				X		X		X	X						16
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PHEOCHROMOCYTOMA						X		X					X	X				X							X	12
THYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-CELL ADENOMA																			X							2
C-CELL CARCINOMA																										1
PARATHYROID	+	+	+	+	-	-	-	-	+	-	+	+	-	-	-	+	+	-	+	-	+	+	+	+	-	25
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ISLET-CELL ADENOMA																								X	X	6
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	+	+	50*
FIBROADENOMA																								X		4
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	X	X	47
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	45
PENIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL PAPILLOMA																										1
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS	X					X					X							X							X	8
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
HEMANGIOMA				X																						1
SPECIAL SENSE ORGANS																										
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL CARCINOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
LEUKEMIA,NOS																	X									1
MYELOMONOCYTIC LEUKEMIA			X		X	X			X			X	X			X										14

* 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 2-BIPHENYLAMINE HYDROCHLORIDE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	105	105	105	105	098	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA											X														
SEBACEOUS ADENOCARCINOMA				X																					
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
FIBROMA																		X							
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, METASTATIC																									
ALVEOLAR/BRONCHIOLAR ADENOMA																						X			
PHEOCHROMOCYTOMA, METASTATIC																X									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS		X																							
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, METASTATIC																									
THYMUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, METASTATIC																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA																									X
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS	X				X			X	X	X							X			X		X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA			X	X	X							X	X		X		X	X			X			
PHEOCHROMOCYTOMA, MALIGNANT																X									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA		X				X																			X
PARATHYROID	-	-	-	+	+	+	+	-	+	-	-	-	+	+	-	-	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA			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	N	N	
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS									X	X															
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,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																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, MALIGNANT																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS, METASTATIC																									
MYELOMONOCYTIC LEUKEMIA																									

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

TABLE 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	084	105	105	105	105	105	104	105	105	105	097	105	105	105	105	098	105	105	105	105	105	102	104	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	X	N	+	+	50*
SQUAMOUS CELL PAPILLOMA																										2
SEBACEOUS ADENOCARCINOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	50*
CARCINOMA,NOS								X																		1
FIBROMA															X											2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA, NOS, METASTATIC								X																		1
ALVEOLAR/BRONCHIOLAR ADENOMA	X		X										X													4
PHEOCHROMOCYTOMA, METASTATIC																										1
TRACHEA	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	-	46
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
MESOTHELIOMA, METASTATIC				X																						1
THYMUS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-	-	43
CIRCULATORY SYSTEM																										
HEART	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, METASTATIC						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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	48
ADENOCARCINOMA, NOS									X																	1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	45
ADENOMA, NOS	X	X	X			X			X		X		X			X	X									17
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA							X	X	X																	12
PHEOCHROMOCYTOMA, MALIGNANT																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL ADENOMA														X		X				X					X	7
PARATHYROID	-	-	+	-	+	-	-	-	-	-	-	+	+	+	-	+	+	-	+	-	+	+	-	+	+	28
ADENOMA, NOS												X														1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA						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	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+		48
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																X				X						4
SPECIAL SENSE ORGANS																										
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA,NOS																										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																								X		1
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
MESOTHELIOMA, MALIGNANT				X																						1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SARCOMA, NOS, METASTATIC																								X		1
MYELOMONOCYTIC LEUKEMIA		X					,																			1

* ANIMALS NECROPSIED

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

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

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	095	104	104	104	082	104	104	104	104	104	104	104	104	104	104	104	104	104	099	104	036	105	104	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA							X																		
BASAL-CELL CARCINOMA				X																					
SUBCUTANEOUS TISSUE	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA		X																							
FIBROMA					X				X																
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA		X																							
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+
THYMUS	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
ESOPHAGUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA																									
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
ADENOMA, NOS		X	X	X		X			X										X						
CRANIOPHARYNGIOMA																		X							
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA											X														X
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
FOLLICULAR-CELL ADENOMA												X													
C-CELL ADENOMA																									
C-CELL CARCINOMA																									
PARATHYROID	-	-	-	-	-	+	+	+	-	-	+	+	-	+	+	+	+	-	-	-	-	+	+	+	-
ADENOMA, NOS															X										
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
ISLET-CELL ADENOMA	X				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
ADENOMA, NOS															X										
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
MESOTHELIOMA, NOS																									
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													
SQUAMOUS CELL PAPILLOMA												X										X			
ADENOMA, NOS	X																								
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N
OSTEOMA								X																	
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MYELOMONOCYTIC LEUKEMIA																			X			X	X		
SCROTUM NOS																									
MESOTHELIOMA, NOS																									

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	103	105	105	105	105	078	105	071	105	096	105	105	105	105	105	105	105	105	071	105	105	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																										1
BASAL-CELL CARCINOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	50*
SQUAMOUS CELL CARCINOMA																			X							1
FIBROMA				X																						4
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA				X											X											2
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	46
LARGE INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA																									X	1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOMA, NOS				X		X					X	X				X							X		X	13
CRANIOPHARYNGIOMA																										1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA						X																				1
PHEOCHROMOCYTOMA	X				X			X						X		X								X		8
THYROID	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	46
FOLLICULAR-CELL ADENOMA																										1
C-CELL ADENOMA							X																			1
C-CELL CARCINOMA	X																									1
PARATHYROID	-	+	-	-	+	+	+	+	-	+	-	+	+	+	+	-	+	-	+	+	+	-	-	+	+	28
ADENOMA, NOS																										1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
ISLET-CELL ADENOMA																										4
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	50*
ADENOMA, NOS																										1
FIBROADENOMA						X																				1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	45
MESOTHELIOMA, NOS									X																	1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	46
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
SQUAMOUS CELL PAPILLOMA																										1
ADENOMA, NOS					X																					4
MUSCULOSKELETAL SYSTEM																										
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
OSTEOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MYELOMONOCYTIC LEUKEMIA																			X							4
SCROTUM NOS																										
MESOTHELIOMA, NOS									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 A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

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	105	105	105	084	106	106	106	106	105	106	106	106	067	105	105	094	106	106	106	106	106	096	105	097
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA													X												
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA													X												
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA	X																					X			
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	-	+	-	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	+	+
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	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA																									
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS		X	X			X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																					X				
THYROID	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
C-CELL ADENOMA																			X						
C-CELL CARCINOMA							X																		
PARATHYROID	-	+	-	-	+	+	+	-	+	+	-	-	+	-	-	+	+	-	-	-	-	-	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	N	N	+	+	+	+	+	+	N	N	+	N	N	+	N	+	+	+	+	+
ADENOCARCINOMA, NOS																									
FIBROADENOMA	X	X	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													
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS							X																		
ENDOMETRIAL STROMAL POLYP	X					X		X														X			X
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
GRANULOSA-CELL TUMOR																									
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														X											
MYELOMONOCYTIC LEUKEMIA					X							X								X			X		
SITE UNKNOWN																									
CARCINOMA,NOS							X																		
HEMATOPOIETIC SYSTEM																									
NEOPLASM, NOS																									

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

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

TABLE 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	106	106	106	098	106	106	106	106	106	106	093	052	101	104	105	106	086	106	106	106	078	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL CARCINOMA															X											1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
THYMUS	+	+	+	-	+	-	+	+	+	+	+	-	-	+	-	-	-	+	+	+	+	+	+	+	+	38
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47
ACINAR-CELL ADENOMA																										1
ESOPHAGUS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	44
STOMACH	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	45
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
TRANSITIONAL-CELL PAPILLOMA																X										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	47
ADENOMA, NOS				X	X			X	X	X	X		X	X			X	X	X		X	X	X	X		33
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA																							X			2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA	X																									1
C-CELL ADENOMA	X		X																							2
C-CELL CARCINOMA					X																					3
PARATHYROID	-	-	+	-	-	-	-	-	+	+	-	-	-	-	-	+	+	+	-	-	+	-	-	-	-	18
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	N	+	+	N	+	N	+	+	+	N	N	N	N	N	N	+	+	+	+	+	N	+	+	N	50*
ADENOCARCINOMA, NOS																								X		1
FIBROADENOMA	X		X	X		X		X	X	X							X	X	X	X			X	X		22
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																								X		3
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
SARCOMA, NOS																										1
ENDOMETRIAL STROMAL POLYP							X															X	X		X	9
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GRANULOSA-CELL TUMOR						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*
LEUKEMIA,NOS																										1
MYELOMONOCYTIC LEUKEMIA																										4
SITE UNKNOWN																										
CARCINOMA,NOS																										1
HEMATOPOIETIC SYSTEM																										
NEOPLASM, NOS																									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 A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	073	105	099	105	105	105	105	105	105	105	105	105	095	105	105	105	105	085	105	105	105
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
THYMUS	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	-	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
C-CELL ADENOMA																				X					
C-CELL CARCINOMA																									
PARATHYROID	+	+	-	+	-	+	+	-	+	+	+	+	-	-	-	-	+	-	-	-	-	+	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	N	N	N	N	+	N	+	N	N	+	N	+	N	N	+	N	+	N	+	N	N	N	+
FIBROADENOMA	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																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	
ADENOCARCINOMA, NOS																									
CYSTADENOMA, NOS																									
SARCOMA, NOS		X																				X			
ENDOMETRIAL STROMAL POLYP																									
ENDOMETRIAL STROMAL SARCOMA																									
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	
THECOMA																									
GRANULOSA-CELL TUMOR																		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															

+: 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	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	104	105	105	105	105	105	105	105	105	105	105	097	086	105	105	105	105	105	105	105	105	
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA																	X								1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	46
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
THYMUS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NEOPLASTIC NODULE				X	X		X																		5
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	-	+	44
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOMA, NOS	X		X			X		X	X	X	X	X	X	X	X		X	X		X	X		X	X	38
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-CELL ADENOMA	X								X			X													4
C-CELL CARCINOMA														X											1
PARATHYROID	+	+	-	-	-	-	-	-	+	+	-	-	-	-	+	+	-	-	-	-	-	+	-	+	19
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA											X				X				X						3
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	N	+	+	N	N	+	N	+	+	N	N	N	+	N	N	+	N	+	N	N	N	N	49*
FIBROADENOMA		X		X														X		X					10
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
ADENOMA, NOS					X																X				2
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOCARCINOMA, NOS					X																				1
CYSTADENOMA, NOS																								X	1
SARCOMA, NOS				X																					1
ENDOMETRIAL STROMAL POLYP	X		X										X												5
ENDOMETRIAL STROMAL SARCOMA									X																1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THECOMA											X														1
GRANULOSA-CELL TUMOR																									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	49*
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	49*
MYELOMONOCYTIC LEUKEMIA																									1

* ANIMALS NECROPSIED

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

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

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	095	105	105	078	105	105	099	105	105	105	105	105	105	104	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA												X													
SARCOMA, NOS												X													
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS														X											
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASM, NOS							X																		
SQUAMOUS CELL CARCINOMA																									
ALVEOLAR/BRONCHIOLAR ADENOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	-	-	-	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	X	X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																	X								
PHEOCHROMOCYTOMA	X				X													X							
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA																									
C-CELL CARCINOMA																									
PARATHYROID	+	-	+	-	+	+	-	+	+	+	+	-	-	-	-	+	+	+	+	-	+	+	+	-	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA															X										
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	N	+	N	+	N	+	N	+	N	+	+	N	N	N	N	N	+	N	N	+	N
ADENOMA, NOS																									
FIBROADENOMA		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
CARCINOMA,NOS																									X
ADENOMA, NOS																					X				
UTERUS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP														X											
ENDOMETRIAL STROMAL SARCOMA															X										
OVARY	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA																									
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
ADENOCA/SQUAMOUS METAPLASIA, META							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																			
SITE UNKNOWN																									
ADENOCA/SQUAMOUS METAPLASIA							X																		

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

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

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

ANIMAL NUMBER	0262	0277	0288	0299	0301	0311	0323	0333	0344	0355	0366	0377	0388	0399	0401	0411	0422	0433	0444	0455	0466	0477	0488	0499	0500	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	102	105	105	105	105	105	087	105	105	105	105	105	105	105	065	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	N	+	+	+	+	50*
SQUAMOUS CELL CARCINOMA																										1
SARCOMA, NOS																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	N	+	+	+	+	50*
SARCOMA, NOS																	X									2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASM, NOS																										1
SQUAMOUS CELL CARCINOMA																					X					1
ALVEOLAR/BRONCHIOLAR ADENOMA				X																						1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	-	+	+	+	+	+	-	-	-	-	+	+	-	+	+	+	+	+	+	-	-	+	+	-	35
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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
ESOPHAGUS	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X		38
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA										X																2
PHEOCHROMOCYTOMA																										3
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL ADENOMA															X											1
C-CELL CARCINOMA																	X					X				2
PARATHYROID	-	-	-	+	-	-	+	+	+	+	+	+	-	-	+	+	+	+	-	+	-	+	+	+	-	31
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	49
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	+	N	N	+	+	N	+	N	N	N	+	N	N	+	N	+	N	+	+	N	+	50*
ADENOMA, NOS																				X						1
FIBROADENOMA					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	50*
CARCINOMA,NOS																										1
ADENOMA, NOS									X																	2
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOMETRIAL STROMAL POLYP		X														X				X			X			5
ENDOMETRIAL STROMAL SARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA	X																									1
BODY CAVITIES																										
PLEURA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOCA/SQUAMOUS METAPLASIA, META																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, HISTIOCYTIC TYPE							X																			1
MYELOMONOCYTIC LEUKEMIA												X														2
SITE UNKNOWN																										
ADENOCA/SQUAMOUS METAPLASIA																										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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

	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)
SEBACEOUS ADENOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
SARCOMA, NOS	4 (8%)	3 (6%)	4 (8%)
FIBROMA		2 (4%)	
FIBROSARCOMA		1 (2%)	
LEIOMYOSARCOMA		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
BILE DUCT CARCINOMA, METASTATIC			1 (2%)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)	4 (8%)
ALVEOLAR/BRONCHIOLAR ADENOMA	14 (28%)	5 (10%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	
SARCOMA, NOS, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	4 (8%)	4 (8%)	4 (8%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#LYMPH NODE	(49)	(47)	(42)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
MALIGNANT LYMPHOMA, NOS		3 (6%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#LIVER	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PEYER'S PATCH	(47)	(48)	(45)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOMA		1 (2%)	
#SPLEEN	(50)	(49)	(47)
HEMANGIOSARCOMA		1 (2%)	
#LYMPH NODE	(49)	(47)	(42)
HEMANGIOMA		1 (2%)	
#LIVER	(50)	(50)	(50)
HEMANGIOMA		1 (2%)	
ANGIOSARCOMA		2 (4%)	3 (6%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(49)	(49)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
#LIVER	(50)	(50)	(50)
BILE DUCT CARCINOMA			1 (2%)
HEPATOCELLULAR ADENOMA	5 (10%)	7 (14%)	1 (2%)
HEPATOCELLULAR CARCINOMA	9 (18%)	12 (24%)	10 (20%)
HEPATOBLASTOMA		1 (2%)	
#STOMACH	(49)	(50)	(47)
BASAL-CELL CARCINOMA	1 (2%)		
#DUODENUM	(47)	(48)	(45)
ADENOCARCINOMA, NOS		1 (2%)	
ADENOMATOUS POLYP, NOS	1 (2%)	1 (2%)	
#JEJUNUM	(47)	(48)	(45)
ADENOCA IN ADENOMATOUS POLYP		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
ADENOCARCINOMA, NOS	1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUBULAR-CELL ADENOMA		1 (2%)	
SARCOMA, NOS, INVASIVE	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(42)	(45)	(39)
ADENOMA, NOS	2 (5%)	1 (2%)	1 (3%)
#ADRENAL	(49)	(49)	(48)
ADENOMA, NOS	3 (6%)	2 (4%)	1 (2%)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	3 (6%)	1 (2%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	2 (4%)	1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SITE UNKNOWN			
ADENOCARCINOMA, NOS		1	
SARCOMA, NOS	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	7	13	27
MORIBUND SACRIFICE	2	2	2
SCHEDULED SACRIFICE	1		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	40	35	21
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	37	38	27
TOTAL PRIMARY TUMORS	54	60	33
TOTAL ANIMALS WITH BENIGN TUMORS	24	20	8
TOTAL BENIGN TUMORS	29	26	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	28	22
TOTAL MALIGNANT TUMORS	25	34	25
TOTAL ANIMALS WITH SECONDARY TUMORS#	4	1	5
TOTAL SECONDARY TUMORS	5	1	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

	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			
*SUBCUT TISSUE	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
SARCOMA, NOS	5 (10%)	1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (12%)	1 (2%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
SARCOMA, NOS, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	6 (12%)	13 (26%)	9 (18%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
#SPLEEN	(48)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	2 (4%)	2 (4%)	
#LYMPH NODE	(40)	(47)	(47)
SARCOMA, NOS, INVASIVE	1 (3%)		
MALIGNANT LYMPHOMA, NOS	1 (3%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (3%)		
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(49)	(50)	(50)
ANGIOSARCOMA			3 (6%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(48)	(49)	(49)
HEMANGIOMA			1 (2%)
ANGIOSARCOMA			1 (2%)
*ADIPOSE TISSUE	(49)	(50)	(50)
ANGIOSARCOMA		1 (2%)	2 (4%)
#LIVER	(49)	(50)	(50)
ANGIOSARCOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
HEPATOCELLULAR ADENOMA	3 (6%)	5 (10%)	4 (8%)
HEPATOCELLULAR CARCINOMA	4 (8%)	4 (8%)	6 (12%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(42)	(41)
ADENOMA, NOS	9 (21%)	8 (19%)	6 (15%)
#ADRENAL	(49)	(47)	(48)
ADENOMA, NOS	1 (2%)	1 (2%)	1 (2%)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(46)	(45)	(48)
FOLLICULAR-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS		1 (2%)	
#UTERUS	(49)	(48)	(49)
ENDOMETRIAL STROMAL POLYP		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#OVARY	(44)	(43)	(44)
CYSTADENOMA, NOS		1 (2%)	
TERATOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(49)	(50)	(50)
ADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
SITE UNKNOWN			
ADENOMA, NOS			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	13	12	18
MORIBUND SACRIFICE	2		4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	5		
TERMINAL SACRIFICE	29	38	28
ANIMAL MISSING	1		

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	31	30	31
TOTAL PRIMARY TUMORS	39	44	44
TOTAL ANIMALS WITH BENIGN TUMORS	19	15	15
TOTAL BENIGN TUMORS	20	19	18
TOTAL ANIMALS WITH MALIGNANT TUMORS	19	20	23
TOTAL MALIGNANT TUMORS	19	24	26
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	
TOTAL SECONDARY TUMORS	2	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

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	105	105	098	105	105	105	105	105	105	105	105	105	105	092	105	105	103	055	100
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SEBACEOUS ADENOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																	X								
SARCOMA, NOS										X										X					
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS, METASTATIC	X																								
HEPATOCELLULAR CARCINOMA, METASTA														X											
ALVEOLAR/BRONCHIOLAR ADENOMA					X												X	X				X			
ALVEOLAR/BRONCHIOLAR CARCINOMA								X																	
SARCOMA, NOS, METASTATIC																									X
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
THYMUS	-	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	-	+	+	-	-	-	-	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA							X		X											X					
HEPATOCELLULAR CARCINOMA								X							X							X		X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	N	+	+	N	N	+	N	N	+	+	+	+	+	+	+	N	+	+	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
BASAL-CELL CARCINOMA																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
ADENOMATOUS POLYP, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS	X																								
SARCOMA, NOS, INVASIVE																				X					
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	-	-	+
ADENOMA, NOS																						X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ADENOMA, NOS					X							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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
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
HEPATOCELLULAR CARCINOMA, METASTA																									X
MALIGNANT LYMPHOMA, NOS			X																						
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
SITE UNKNOWN																									
SARCOMA, NOS																									X

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	107	102	105	027	105	105	105	105	105	105	105	105	105	083	105	105	105	105	090	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SEBACEOUS ADENOMA													X													1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL CARCINOMA																										1
SARCOMA, NOS			X	X																						4
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS, METASTATIC																										1
HEPATOCELLULAR CARCINOMA, METASTA																										1
ALVEOLAR/BRONCHIOLAR ADENOMA							X	X	X				X				X	X			X	X	X		X	14
ALVEOLAR/BRONCHIOLAR CARCINOMA																			X							2
SARCOMA, NOS, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	45
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																X										1
THYMUS	+	-	-	-	+	-	-	-	-	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+	29
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA				X															X							5
HEPATOCELLULAR CARCINOMA						X								X				X	X	X					X	9
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	N	N	+	N	N	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
BASAL-CELL CARCINOMA									X																	1
SMALL INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
ADENOMATOUS POLYP, NOS																									X	1
LARGE INTESTINE	+	-	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																										1
SARCOMA, NOS, INVASIVE																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	42
ADENOMA, NOS							X																			2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS										X																3
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	46
PARATHYROID	+	-	+	+	-	-	-	-	-	+	+	-	-	-	+	-	-	-	-	+	+	-	-	-	+	21
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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						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
HEPATOCELLULAR CARCINOMA, METASTA																										1
MALIGNANT LYMPHOMA, NOS					X	X									X									X		4
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
SITE UNKNOWN																										
SARCOMA, NOS																										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 2-BIPHENYLAMINE HYDROCHLORIDE

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	015	041	069	041	041	032	040	041	055	055	055	066	051	011	055	055	047	055	051	000	055	055	055	055	055
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROMA		X							X																
FIBROSARCOMA					X																				
LEIOMYOSARCOMA														X											
HEMANGIOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																									
ALVEOLAR/BRONCHIOLAR ADENOMA				X				X										X							
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA										X															
MALIGNANT LYMPHOMA, NOS					X															X					
THYMUS	-	-	+	+	-	-	+	-	+	-	+	-	+	-	+	+	-	-	+	-	+	-	-	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA				X										X	X		X			X					
HEPATOCELLULAR CARCINOMA			X				X																	X	X
HEPATOBLASTOMA																									
HEMANGIOMA																									
ANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ADENOCARCINOMA, NOS																									
ADENOMATOUS POLYP, NOS											X														
ADENOCA IN ADENOMATOUS POLYP																									
MALIGNANT LYMPHOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA																			X						
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
PHEOCHROMOCYTOMA																									
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	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
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														
SITE UNKNOWN																									
ADENOCARCINOMA, NOS																									

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

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	099	105	105	105	105	087	078	071	081	075	105	105	105	105	105	105	101	097	095	105	100	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS	X			X																X						3
FIBROMA																										2
FIBROSARCOMA																										1
LEIOMYOSARCOMA																	X									2
HEMANGIOMA					X																					1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA								X																		1
ALVEOLAR/BRONCHIOLAR ADENOMA											X								X							5
ALVEOLAR/BRONCHIOLAR CARCINOMA																								X		1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA						X																				1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		47
HEMANGIOMA																										1
MALIGNANT LYMPHOMA, NOS															X											3
THYMUS	-	-	-	-	-	-	-	-	-	+	-	+	+	+	+	+	-	-	+	-	-	-	+	+	-	20
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA			X																X							7
HEPATOCELLULAR CARCINOMA					X	X		X					X							X	X	X		X		12
HEPATOBLASTOMA										X																1
HEMANGIOMA								X																		1
ANGIOSARCOMA					X	X																				2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	●	●	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOCARCINOMA, NOS												X														1
ADENOMATOUS POLYP, NOS																										1
ADENOCA IN ADENOMATOUS POLYP																									X	1
MALIGNANT LYMPHOMA, NOS																			X							1
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	45
ADENOMA, NOS		X																								1
ADRENAL	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS			X	X																						2
PHEOCHROMOCYTOMA					X					X							X									3
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
PARATHYROID	+	+	-	+	+	+	-	+	-	+	+	+	+	-	+	-	-	-	+	+	+	+	+	-	+	32
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																										1
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																							4
SITE UNKNOWN																										
ADENOCARCINOMA, NOS																		X								1

* ANIMALS NECROPSIED

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

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

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	104	104	093	083	104	056	104	104	104	032	062	000	104	104	084	080	104	092	081	104	041	087	081	104	111
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																X						X		X	X
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT CARCINOMA, METASTATIC				X																					
HEPATOCELLULAR CARCINOMA, METASTA				X																					
ALVEOLAR/BRONCHIOLAR ADENOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	-	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA				X																					
MALIGNANT LYMPHOMA, NOS																	X								
THYMUS	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																					X				
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT CARCINOMA				X																					
HEPATOCELLULAR ADENOMA																									
HEPATOCELLULAR CARCINOMA				X								X	X		X						X				
ANGIOSARCOMA																					X				
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	N	N	+	+	+	+	+	N	N	N	N	+	N	+	+	+	N	+	+	+	N	N	+
PANCREAS	+	+	+	-	+	-	+	+	+	+	+	+	+	-	+	+	+	-	-	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
MALIGNANT LYMPHOMA, NOS													X												
LARGE INTESTINE	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	-	+	+	-	-	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	-	+	-	+	-	+	+	+	+
ADENOMA, NOS									X																
ADRENAL	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
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	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																						X	X		
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
BILE DUCT CARCINOMA, METASTATIC				X																					
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS																				X					

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

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) 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	003	006	009	010	010	010	008	010	011	010	010	010	009	011	010	009	009	009	009	010	010	010	010	010	010	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE SARCOMA, NOS	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	50M 4
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT CARCINOMA, METASTATIC																										1
HEPATOCELLULAR CARCINOMA, METASTA													X			X				X						4
ALVEOLAR/BRONCHIOLAR ADENOMA																									X	1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		47
SPLEEN	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
LYMPH NODES	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+		42
HEPATOCELLULAR CARCINOMA, METASTA																										1
MALIGNANT LYMPHOMA, NOS																										1
THYMUS	-	-	-	-	+	-	-	-	-	+	-	+	-	+	-	-	-	-	-	-	-	+	-	+		8
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
HEPATOCELLULAR CARCINOMA, METASTA																										1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
BILE DUCT CARCINOMA																										1
HEPATOCELLULAR ADENOMA																		X								1
HEPATOCELLULAR CARCINOMA		X		X			X						X			X				X					X	10
ANGIOSARCOMA																										3
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																					X					1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
GALLBLADDER & COMMON BILE DUCT	N	N	+	+	+	+	N	+	N	+	+	+	N	+	+	+	+	N	+	N	N	N	+	N	+	50M
PANCREAS	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		42
ESOPHAGUS	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-		47
STOMACH	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
SMALL INTESTINE	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
MALIGNANT LYMPHOMA, NOS																										1
LARGE INTESTINE	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+		41
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
URINARY BLADDER	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+		47
ENDOCRINE SYSTEM																										
PITUITARY	-	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	-	+		39
ADENOMA, NOS																										1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+		48
ADENOMA, NOS																	X									1
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
PARATHYROID	+	+	+	+	-	+	-	-	+	+	-	-	+	-	+	-	+	+	-	+	+	+	+	-		32
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		50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		47
PROSTATE	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
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		50M
ADENOMA, NOS																										2
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		50M
BILE DUCT CARCINOMA, METASTATIC																										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		50M
MALIGNANT LYMPHOMA, NOS			X			X																X				4

* ANIMALS NECROPSIED

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

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

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	102	105	105	101	105	105	105	105	105	085	105	100	105	092	105	105	105	105	105	105	105	105	084	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+ X	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	M	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA SARCOMA, NOS, METASTATIC	+	+	+ X	+ X X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	-	+	+	-	+	-	+	+	-	+	+	-	+	-	M	+	+
SPLEEN MALIGNANT LYMPHOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+ X	+	+	+	+	M	+	+
LYMPH NODES SARCOMA, NOS, INVASIVE MALIGNANT LYMPHOMA, NOS MALIG.LYMPHOMA, HISTIOCYTIC TYPE	+	+ X	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	M	+	-
THYMUS	-	-	-	-	+	-	+	+	+	+	-	-	+	-	+	+	-	+	+	+	-	+	M	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+	+	M	+	+
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	+ X	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+ X	+ X	+ X	+	+	+	M	+ X	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	+	N	+	+	+	N	+	N	+	N	+	N	+	+	+	+	+	+	+	+	M	+	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	M	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	M	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	M	+	+
LARGE INTESTINE	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	M	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	M	+	+
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	+	+ X	+	+ X	+ X	+	+	+	+	+	+	+	+	-	+	+ X	+	+	+ X	-	+	M	+	+
ADRENAL ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	M	+	+
THYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	M	+	+
PARATHYROID	+	+	+	+	+	-	-	-	-	+	+	-	-	-	+	+	-	+	+	-	+	+	M	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	M	N	N
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
OVARY	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	M	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N X	N	N X	N	N X	N	N	N	N	N	N	M	N	N

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	102	097	105	085	085	085	085	085	102	105	105	087	105	105	105	105	094	074	102	061	083	094	067	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
SARCOMA, NOS		X	X		X						X															5
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA	X												X	X										X		6
SARCOMA, NOS, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	41
SPLEEN	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
MALIGNANT LYMPHOMA, NOS																										2
LYMPH NODES	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	-	+	-	40
SARCOMA, NOS, INVASIVE					X																					1
MALIGNANT LYMPHOMA, NOS															X											1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
THYMUS	+	+	-	-	-	-	-	-	-	-	-	+	-	-	-	+	+	+	+	+	-	+	-	-	+	23
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+		45
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA								X																		3
HEPATOCELLULAR CARCINOMA																										4
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	N	N	N	N	N	N	+	+	N	+	+	+	+	+	+	N	N	N	N	N	49*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+		47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
STOMACH	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+		44
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	+	-			42
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	-	+	-	+		43
ADENOMA, NOS		X										X			X			X								9
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
ADENOMA, NOS																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-		46
PARATHYROID	-	+	-	+	+	+	+	-	+	+	+	+	+	+	-	+	-	+	+	-	+	-	+	-		30
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		49*
ADENOMA, NOS				X																						1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
OVARY	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		49*
MALIGNANT LYMPHOMA, NOS														X					X		X					6

* 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 2-BIPHENYLAMINE HYDROCHLORIDE

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	087	105	105	105	105	101	105	105	105	105	105	082	105	105	105	105	105	105	096	105	040	076	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI HEPATOCELLULAR CARCINOMA, METASTA ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+
SPLEEN MALIGNANT LYMPHOMA, NOS	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	
THYMUS	+	-	-	-	-	+	+	-	-	+	+	-	-	+	+	-	+	+	-	-	-	+	-	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+ X	+ X	+ X	+ X	+	+	+	+	+	+	+ X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	-	-	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	+ X	+	+	+	+	+	-	+	+	+ X	+	+	-	+	+ X	+ X	+	+	+	+	-	+	-	+
ADRENAL ADENOMA, NOS PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	-	+
THYROID	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+
PARATHYROID	-	+	-	+	+	+	+	+	-	+	-	+	-	+	-	-	-	+	-	+	+	+	-	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, 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 X	N
UTERUS ENDOMETRIAL STROMAL POLYP	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY CYSTADENOMA, NOS TERATOMA, NOS	+	+	+ X	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+ X	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS MALIG.LYMPHOMA, HISTIOCYTIC TYPE	N	N	N X	N X	N	N	N	N	N	N	N	N	N	N X	N	N X	N X	N	N	N	N	N	N	N X	N
ADIPOSE TISSUE ANGIOSARCOMA																									

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	093	105	105	105	083	105	082	105	105	071	096	105	105	105	105	105	105	105	105	105	105	082	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS																					X					1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA											X															1
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	46
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIGNANT LYMPHOMA, NOS		X																								2
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
THYMUS	–	–	–	–	+	–	+	–	+	+	–	–	–	+	+	–	+	–	+	–	+	+	+	–	–	22
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA						X	X				X															5
HEPATOCELLULAR CARCINOMA																										4
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	+	N	+	N	+	+	N	N	+	+	+	+	+	+	+	+	N	N	+		50*
PANCREAS	+	+	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	–	+	–	+		42
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+		47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+		49
SMALL INTESTINE	+	+	–	+	+	+	–	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+		41
LARGE INTESTINE	+	+	+	+	+	+	–	+	–	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+		45
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+		49
URINARY BLADDER	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+		45
ENDOCRINE SYSTEM																										
PITUITARY	+	+	–	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+		42
ADENOMA, NOS		X			X						X										X					8
ADRENAL	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+		47
ADENOMA, NOS																										1
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–		45
PARATHYROID	+	–	–	–	+	+	+	+	–	+	+	–	+	+	–	–	+	–	+	+	–	–	+	–	–	27
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N		50*
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–		48
ENDOMETRIAL STROMAL POLYP																										1
OVARY	–	+	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	–	+			43
CYSTADENOMA, NOS																										1
TERATOMA, NOS																										1
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50*
ADENOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50*
MALIGNANT LYMPHOMA, NOS			X			X	X		X					X								X	X			13
MALIG.LYMPHOMA, HISTIOCYTIC TYPE													X											X		2
ADIPOSE TISSUE																										
ANGIOSARCOMA											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

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF 2-BIPHENYLAMINE HYDROCHLORIDE

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	102	104	104	104	104	104	104	104	097	091	104	087	078	082	041	041	041	041	041	041	041	041	044	044	044
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																X			X		X				
SARCOMA, NOS																									
ANGIOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA	X					X															X				
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA						X																			
ANGIOSARCOMA											X														
LYMPH NODES	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	+	+	-	+	+	-	+	+	-	-	-	+	+	+	-	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA		X	X	X																					
HEPATOCELLULAR CARCINOMA	X						X																X		
ANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	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		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									X
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	+	+	+	-	+	+	-	+	+	-	+	+	-	-	+	+	+	+	+	+	+	-	-	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	+	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
OVARY	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+
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	
SITE UNKNOWN																									
ADENOMA, NOS																									
ADIPOSE TISSUE																									
ANGIOSARCOMA		X																						X	

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

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	100	060	104	084	049	083	074	104	093	067	104	117	086	058	084	094	091	097	094	078	044	041	087	067	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL CARCINOMA													X													1
SARCOMA, NOS										X																2
ANGIOSARCOMA							X																			3
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA											X															4
ALVEOLAR/BRONCHIOLAR CARCINOMA																									X	1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOMA																										1
ANGIOSARCOMA																										1
LYMPH NODES	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47
THYMUS	+	-	-	+	+	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	-	-	-	-	-	23
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+		49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA									X																	4
HEPATOCELLULAR CARCINOMA													X						X		X					6
ANGIOSARCOMA																					X					1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	N	N	N	N	N	N	+	+	N	+	N	N	+	+	+	+	+	N	+	+	+	+	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+		48
ESOPHAGUS	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-		46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
SMALL INTESTINE	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-		44
LARGE INTESTINE	+	-	+	+	+	-	+	+	+	-	-	+	+	+	+	+	+	+	+	-	+	+	-	-		39
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
URINARY BLADDER	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+		46
ENDOCRINE SYSTEM																										
PITUITARY	-	+	-	-	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+		41
ADENOMA, NOS																										6
ADRENAL	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
ADENOMA, NOS																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+		48
FOLLICULAR-CELL ADENOMA																	X									1
PARATHYROID	+	-	-	+	-	+	+	-	-	-	+	-	-	+	+	-	+	+	+	-	+	-	+	+		31
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50*
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+		44
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50*
MALIGNANT LYMPHOMA, NOS		X	X		X									X				X				X				9
SITE UNKNOWN																										
ADENOMA, NOS																X										1
ADIPOSE TISSUE																										
ANGIOSARCOMA																										2

* ANIMALS NECROPSIED

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

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

	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%)	
INFLAMMATION, NOS		1 (2%)	1 (2%)
HYPERPLASIA, BASAL CELL		2 (4%)	1 (2%)
HYPERKERATOSIS	2 (4%)	1 (2%)	1 (2%)
ACANTHOSIS	1 (2%)	1 (2%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(49)	(50)
BRONCHIECTASIS			1 (2%)
INFLAMMATION, NOS			1 (2%)
#LUNG	(50)	(49)	(50)
INFLAMMATION, NOS	2 (4%)	2 (4%)	4 (8%)
INFLAMMATION, FOCAL		1 (2%)	
REACTION, FOREIGN BODY	1 (2%)	1 (2%)	3 (6%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(48)	(50)	(50)
INFARCT, NOS		1 (2%)	
HEMATOPOIESIS	8 (17%)	17 (34%)	4 (8%)
#LUMBAR LYMPH NODE	(48)	(49)	(48)
PLASMACYTOSIS			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(49)	(50)	(50)
HEMATOPOIESIS	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(49)	(50)
MINERALIZATION		1 (2%)	
THROMBOSIS, NOS	1 (2%)		
INFLAMMATION, NOS		1 (2%)	
FIBROSIS	2 (4%)	1 (2%)	1 (2%)
#AURICULAR APPENDAGE	(50)	(49)	(50)
THROMBOSIS, NOS	1 (2%)		
#MYOCARDIUM	(50)	(49)	(50)
DEGENERATION, NOS	34 (68%)	36 (73%)	38 (76%)
*PANCREATIC ARTERY	(50)	(50)	(50)
PERIVASCULITIS		3 (6%)	6 (12%)
*RENAL ARTERY	(50)	(50)	(50)
PERIVASCULITIS		1 (2%)	1 (2%)
#STOMACH	(47)	(50)	(49)
PERIVASCULITIS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
DILATATION, NOS	1 (2%)		
FIBROSIS	1 (2%)		
NECROSIS, FOCAL	5 (10%)	2 (4%)	3 (6%)
NECROSIS, ISCHEMIC	2 (4%)		
INFARCT, NOS		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)		3 (6%)
BASOPHILIC CYTO CHANGE	6 (12%)	11 (22%)	10 (20%)
FOCAL CELLULAR CHANGE	12 (24%)	23 (46%)	22 (44%)
CLEAR-CELL CHANGE	1 (2%)	1 (2%)	1 (2%)
#BILE DUCT	(49)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	1 (2%)
#PANCREATIC ACINUS	(48)	(50)	(47)
ATROPHY, NOS	1 (2%)	1 (2%)	2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ATROPHY, FOCAL		2 (4%)	
#STOMACH	(47)	(50)	(49)
INFLAMMATION, NOS	3 (6%)		
NECROSIS, NOS	4 (9%)		1 (2%)
HYPERPLASIA, BASAL CELL	7 (15%)	3 (6%)	3 (6%)
HYPERKERATOSIS	2 (4%)	1 (2%)	3 (6%)
ACANTHOSIS	3 (6%)	1 (2%)	3 (6%)
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
MINERALIZATION		4 (8%)	4 (8%)
INFLAMMATION, NOS	21 (43%)	43 (86%)	41 (82%)
FIBROSIS, DIFFUSE	15 (31%)	41 (82%)	40 (80%)
NEPHROPATHY	46 (94%)	50 (100%)	49 (98%)
DEGENERATION, CYSTIC		1 (2%)	6 (12%)
#KIDNEY/PELVIS	(49)	(50)	(50)
HYPERPLASIA, EPITHELIAL	3 (6%)	8 (16%)	9 (18%)
#URINARY BLADDER	(48)	(50)	(47)
INFLAMMATION, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(45)	(48)
DILATATION, NOS			2 (4%)
#ADRENAL	(48)	(50)	(49)
MINERALIZATION	1 (2%)		
HEMORRHAGE			1 (2%)
METAPLASIA, OSSEOUS			1 (2%)
#ADRENAL CORTEX	(48)	(50)	(49)
HYPERTROPHY, FOCAL		1 (2%)	
HYPERPLASIA, NOS			2 (4%)
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(48)	(50)	(49)
HYPERPLASIA, NODULAR			4 (8%)
HYPERPLASIA, NOS	3 (6%)	1 (2%)	1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(47)	(49)	(46)
FOLLICULAR CYST, NOS			1 (2%)
HYPERPLASIA, C-CELL	1 (2%)	4 (8%)	5 (11%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	1 (2%)		
*PENIS	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
*PREPUCE	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)	1 (2%)	1 (2%)
FIBROSIS	1 (2%)		1 (2%)
NECROSIS, NOS	3 (6%)	1 (2%)	3 (6%)
#PROSTATE	(45)	(48)	(46)
INFLAMMATION, NOS	1 (2%)		2 (4%)
#TESTIS	(49)	(50)	(49)
MINERALIZATION	2 (4%)	3 (6%)	8 (16%)
ATROPHY, NOS	1 (2%)	2 (4%)	2 (4%)
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)		2 (4%)
NERVOUS SYSTEM			
#BRAIN	(50)	(49)	(50)
HEMORRHAGE			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
OMENTUM			
MINERALIZATION			1
NECROSIS, FAT			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
HYPERPLASIA, BASAL CELL		1 (2%)	
HYPERKERATOSIS	1 (2%)		1 (2%)
ACANTHOSIS			1 (2%)
*SUBCUT TISSUE	(50)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(49)	(50)
HYPERPLASIA, NOS			1 (2%)
#LUNG	(50)	(49)	(50)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS	2 (4%)	5 (10%)	1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(48)	(49)	(50)
HEMOSIDEROSIS		1 (2%)	
HYPERPLASIA, RETICULUM CELL			1 (2%)
HEMATOPOIESIS	19 (40%)	31 (63%)	19 (38%)
#LIVER	(50)	(49)	(50)
HEMATOPOIESIS	3 (6%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(49)	(50)
INFLAMMATION, NOS	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FIBROSIS	1 (2%)		
#MYOCARDIUM	(50)	(49)	(50)
DEGENERATION, NOS	18 (36%)	20 (41%)	19 (38%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
DILATATION, NOS	2 (4%)		
FIBROSIS	1 (2%)		
NECROSIS, FOCAL	3 (6%)	5 (10%)	1 (2%)
NECROSIS, ISCHEMIC			1 (2%)
METAMORPHOSIS FATTY	3 (6%)	3 (6%)	4 (8%)
BASOPHILIC CYTO CHANGE	36 (72%)	29 (59%)	39 (78%)
FOCAL CELLULAR CHANGE	2 (4%)	9 (18%)	5 (10%)
#BILE DUCT	(50)	(49)	(50)
HYPERPLASIA, NOS			1 (2%)
#PANCREATIC ACINUS	(47)	(49)	(49)
ATROPHY, NOS	2 (4%)	2 (4%)	1 (2%)
HYPERTROPHY, FOCAL	1 (2%)		
#STOMACH	(47)	(49)	(49)
INFLAMMATION, NOS	1 (2%)		
HYPERPLASIA, BASAL CELL	3 (6%)	3 (6%)	
HYPERKERATOSIS	4 (9%)	3 (6%)	
ACANTHOSIS	2 (4%)	4 (8%)	
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(50)
MINERALIZATION	12 (24%)	7 (14%)	11 (22%)
INFLAMMATION, NOS	3 (6%)	4 (8%)	6 (12%)
GLOMERULONEPHRITIS, FOCAL	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)	1 (2%)	
FIBROSIS, DIFFUSE		2 (4%)	6 (12%)
NEPHROPATHY	26 (52%)	37 (76%)	43 (86%)
DEGENERATION, CYSTIC		1 (2%)	
GLOMERULOSCLEROSIS, NOS		1 (2%)	
#KIDNEY/PELVIS	(50)	(49)	(50)
HYPERPLASIA, EPITHELIAL	2 (4%)		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	(47)	(48)	(50)
CYST, NOS	1 (2%)		
ANGIECTASIS	1 (2%)	2 (4%)	1 (2%)
#ADRENAL	(50)	(49)	(50)
MINERALIZATION	1 (2%)	1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	
#ADRENAL CORTEX	(50)	(49)	(50)
HYPERTROPHY, FOCAL		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)
#ADRENAL MEDULLA	(50)	(49)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	2 (4%)
#THYROID	(49)	(47)	(49)
FOLLICULAR CYST, NOS		1 (2%)	1 (2%)
HYPERPLASIA, C-CELL		6 (13%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
GALACTOCELE	9 (18%)	3 (6%)	5 (10%)
INFLAMMATION, NOS	2 (4%)		
HYPERPLASIA, NOS			1 (2%)
*CLITORAL GLAND	(50)	(49)	(50)
NECROSIS, NOS	1 (2%)	1 (2%)	1 (2%)
#UTERUS	(49)	(47)	(48)
HYDROMETRA	2 (4%)		1 (2%)
INFLAMMATION, NOS	1 (2%)	1 (2%)	2 (4%)
PYOMETRA			1 (2%)
#UTERUS/ENDOMETRIUM	(49)	(47)	(48)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
#OVARY	(49)	(48)	(49)
CYST, NOS			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(49)	(49)	(50)
HEMORRHAGE	1 (2%)		1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(49)	(50)
HYPEROSTOSIS	1 (2%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
MINERALIZATION		1 (2%)	
OMENTUM			
NECROSIS, FAT	6	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 FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

	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)
NECROSIS, NOS		1 (2%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	1 (2%)
REACTION, FOREIGN BODY			1 (2%)
NECROSIS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(50)
INFLAMMATION, NOS	11 (22%)	21 (42%)	3 (6%)
#LUNG	(50)	(50)	(50)
MINERALIZATION	3 (6%)	2 (4%)	
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS	18 (36%)	29 (58%)	11 (22%)
PNEUMONIA, ASPIRATION			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)	9 (18%)	2 (4%)
#BONE MARROW	(45)	(48)	(47)
HYPERPLASIA, HEMATOPOIETIC	3 (7%)	2 (4%)	3 (6%)
#SPLEEN	(50)	(49)	(47)
HYPERPLASIA, LYMPHOID	1 (2%)		1 (2%)
HEMATOPOIESIS	14 (28%)	8 (16%)	12 (26%)
#LYMPH NODE	(49)	(47)	(42)
HEMORRHAGE		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
REACTION, FOREIGN BODY	1 (2%)		
ANGIECTASIS		7 (15%)	1 (2%)
PLASMACYTOSIS			3 (7%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
HEMATOPOIESIS	4 (8%)	12 (26%)	8 (19%)
#MEDIASTINAL L.NODE	(49)	(47)	(42)
HYPERPLASIA, NOS	1 (2%)		
#LUMBAR LYMPH NODE	(49)	(47)	(42)
PLASMACYTOSIS		1 (2%)	1 (2%)
#MESENTERIC L. NODE	(49)	(47)	(42)
ANGIECTASIS	2 (4%)		
HYPERPLASIA, RETICULUM CELL			1 (2%)
HEMATOPOIESIS	6 (12%)	1 (2%)	1 (2%)
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
ENDOCARDITIS, BACTERIAL			2 (4%)
FIBROSIS			1 (2%)
#ENDOCARDIUM	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
#CARDIAC VALVE	(50)	(50)	(50)
INFLAMMATION, NOS			2 (4%)
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
#LIVER	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
DILATATION, NOS	2 (4%)		
NECROSIS, NOS		1 (2%)	1 (2%)
NECROSIS, FOCAL	1 (2%)	2 (4%)	3 (6%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, ISCHEMIC		1 (2%)	1 (2%)
METAMORPHOSIS FATTY	3 (6%)	3 (6%)	2 (4%)
BASOPHILIC CYTO CHANGE			1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)		
EOSINOPHILIC CYTO CHANGE	1 (2%)		
CLEAR-CELL CHANGE	1 (2%)	1 (2%)	
*GALLBLADDER	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
#PANCREAS	(48)	(49)	(42)
INFLAMMATION, NOS		1 (2%)	
#PANCREATIC ACINUS	(48)	(49)	(42)
ATROPHY, NOS		1 (2%)	
HYPERTROPHY, FOCAL			1 (2%)
#STOMACH	(49)	(50)	(47)
HEMORRHAGE	1 (2%)		
INFLAMMATION, NOS	2 (4%)	2 (4%)	1 (2%)
HYPERKERATOSIS	1 (2%)	1 (2%)	1 (2%)
#GASTRIC MUCOSA	(49)	(50)	(47)
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)
#JEJUNUM	(47)	(48)	(45)
INFLAMMATION, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
MINERALIZATION	6 (12%)	3 (6%)	1 (2%)
HYDRONEPHROSIS			1 (2%)
INFLAMMATION, NOS		1 (2%)	1 (2%)
INFLAMMATION, INTERSTITIAL	2 (4%)		
ABSCESS, NOS			1 (2%)
NEPHROPATHY		2 (4%)	
#PERIRENAL TISSUE	(50)	(50)	(49)
ABSCESS, NOS			1 (2%)
#URINARY BLADDER	(50)	(50)	(47)
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
ENDOCRINE SYSTEM			
#ADRENAL	(49)	(49)	(48)
MINERALIZATION		1 (2%)	
HYPERPLASIA, NOS	2 (4%)	7 (14%)	
#ADRENAL CORTEX	(49)	(49)	(48)
HYPERTROPHY, FOCAL	3 (6%)	1 (2%)	
#THYROID	(46)	(46)	(49)
INFLAMMATION, NOS	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		
REPRODUCTIVE SYSTEM			
*PENIS	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		3 (6%)
NECROSIS, NOS			1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
NECROSIS, NOS		1 (2%)	
*SEMINAL VESICLE	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
#TESTIS	(50)	(49)	(47)
MINERALIZATION	1 (2%)	1 (2%)	1 (2%)
*EPIDIDYMIS	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
OMENTUM			
NECROSIS, FAT	2		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	2	6

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

	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			
*SUBCUT TISSUE	(49)	(50)	(50)
MINERALIZATION		1 (2%)	
INFLAMMATION, NOS			1 (2%)
ABSCESS, NOS		1 (2%)	
NECROSIS, NOS		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(49)	(50)	(50)
INFLAMMATION, NOS	4 (8%)	5 (10%)	4 (8%)
#LUNG	(49)	(50)	(50)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS	10 (20%)	10 (20%)	10 (20%)
INFLAMMATION, ACUTE	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
HEMATOPOIESIS	2 (4%)	7 (14%)	2 (4%)
*SUBCUT TISSUE	(49)	(50)	(50)
HEMATOPOIESIS			1 (2%)
#BONE MARROW	(41)	(46)	(47)
HYPERPLASIA, HEMATOPOIETIC	2 (5%)		3 (6%)
MYELOPOIESIS			1 (2%)
#SPLEEN	(48)	(49)	(49)
HEMATOPOIESIS	21 (44%)	19 (39%)	23 (47%)
#LYMPH NODE	(40)	(47)	(47)
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
ANGIECTASIS		2 (4%)	
PLASMACYTOSIS		1 (2%)	1 (2%)
HEMATOPOIESIS	3 (8%)	1 (2%)	1 (2%)
#LUMBAR LYMPH NODE	(40)	(47)	(47)
HEMORRHAGIC CYST			1 (2%)
PLASMACYTOSIS			1 (2%)
HEMATOPOIESIS			1 (2%)
#MESENTERIC L. NODE	(40)	(47)	(47)
ANGIECTASIS			1 (2%)
HEMATOPOIESIS	3 (8%)		3 (6%)
#RENAL LYMPH NODE	(40)	(47)	(47)
PLASMACYTOSIS		1 (2%)	
HEMATOPOIESIS	1 (3%)		
#LIVER	(49)	(50)	(50)
HEMATOPOIESIS	4 (8%)		6 (12%)
#ADRENAL	(49)	(47)	(48)
HEMATOPOIESIS	1 (2%)	1 (2%)	
CIRCULATORY SYSTEM			
#LYMPH NODE	(40)	(47)	(47)
THROMBOSIS, NOS		1 (2%)	
#MESENTERIC L. NODE	(40)	(47)	(47)
THROMBOSIS, NOS			1 (2%)
#HEART	(49)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
#AURICULAR APPENDAGE	(49)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#UTERUS	(49)	(48)	(49)
THROMBOSIS, NOS			1 (2%)
#OVARY	(44)	(43)	(44)
THROMBOSIS, NOS	2 (5%)		
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
DILATATION, NOS	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
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL	4 (8%)		3 (6%)
NECROSIS, COAGULATIVE	1 (2%)		
NECROSIS, ISCHEMIC			2 (4%)
METAMORPHOSIS FATTY	4 (8%)	6 (12%)	2 (4%)
*GALLBLADDER	(49)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
#PANCREAS	(47)	(42)	(48)
MINERALIZATION	1 (2%)		
INFLAMMATION, NOS	1 (2%)		
#PANCREATIC ACINUS	(47)	(42)	(48)
ATROPHY, NOS	1 (2%)	3 (7%)	
#STOMACH	(47)	(49)	(49)
MINERALIZATION		1 (2%)	
INFLAMMATION, NOS	1 (2%)	3 (6%)	
ULCER, NOS			1 (2%)
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL		1 (2%)	
HYPERPLASIA, BASAL CELL	1 (2%)		
HYPERKERATOSIS	7 (15%)	1 (2%)	1 (2%)
ACANTHOSIS		1 (2%)	
#PEYER'S PATCH	(44)	(41)	(44)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(50)
MINERALIZATION		1 (2%)	1 (2%)
GLOMERULONEPHRITIS, NOS			1 (2%)
INFLAMMATION, NOS		1 (2%)	
ABSCESS, NOS	2 (4%)		
NEPHROPATHY		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(42)	(41)
HYPERPLASIA, NOS			1 (2%)
#ADRENAL	(49)	(47)	(48)
DEGENERATION, LIPOID		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
HYPERPLASIA, NOS	1 (2%)	6 (13%)	4 (8%)
#THYROID	(46)	(45)	(48)
FOLLICULAR CYST, NOS			1 (2%)
HYPERPLASIA, FOLLICULAR-CELL		2 (4%)	
REPRODUCTIVE SYSTEM			
*VULVA	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)	1 (2%)	
ACANTHOSIS	1 (2%)		
*VAGINA	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
ACANTHOSIS	1 (2%)		
#UTERUS	(49)	(48)	(49)
HYDROMETRA	5 (10%)	8 (17%)	2 (4%)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS	2 (4%)	7 (15%)	7 (14%)
PYOMETRA	1 (2%)		
ABSCESS, NOS	2 (4%)	1 (2%)	1 (2%)
NECROSIS, NOS			1 (2%)
#CERVIX UTERI	(49)	(48)	(49)
INFLAMMATION, NOS	1 (2%)	1 (2%)	
#UTERUS/ENDOMETRIUM	(49)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, NOS	4 (8%)	2 (4%)	2 (4%)
HYPERPLASIA, CYSTIC	20 (41%)	23 (48%)	18 (37%)
#OVARY	(44)	(43)	(44)
MINERALIZATION	1 (2%)		1 (2%)
HEMORRHAGE			2 (5%)
INFLAMMATION, NOS	1 (2%)	1 (2%)	
ABSCESS, NOS	7 (16%)	3 (7%)	8 (18%)
FIBROSIS			4 (9%)
DEGENERATION, CYSTIC			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(50)
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
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(49)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(50)	(50)
ABSCESS, NOS			1 (2%)
*PERITONEUM	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
OMENTUM			
NECROSIS, FAT	3	1	2
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	2
ANIMAL MISSING/NO NECROPSY	1		

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

APPENDIX E

ANALYSIS OF TECHNICAL-GRADE 2-BIPHENYLAMINE (LOT NO. 081547) MIDWEST RESEARCH INSTITUTE

APPENDIX E

A. ELEMENTAL ANALYSIS

Element	C	H	N
Theory	85.17	6.55	8.28
Determined	85.27	6.55	8.17
	85.11	6.57	8.19

B. MELTING POINT

Determined	Literature Values
44°-47°C (visual, sealed, evacuated capillary)	45°C (Finzi and Leandri, 1950)

C. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel F-254

Amount Spotted: 120 and 360 μg

Ref. Standard: Aniline

Visualization: Ultraviolet, 254 and 366 nm

System 1: Chloroform, 100%

R_f: 0.34, 0.19 (minor, 254 nm only), origin (minor, 366 nm only)

R_{st}: 2.00, 1.12, origin

System 2: Ethyl acetate, 100%

R_f: 0.95, 0.89 (minor, 254 nm only), origin (minor, 366 nm only)

R_{st}: 1.07, 1.00, origin

D. VAPOR-PHASE CHROMATOGRAPHY

System 1:

Instrument: Tracor MT-220
Column: 3% OV-1 on 80/100 Supelcoport, 1.8 m x 4 mm I.D.
Detector: Flame ionization
Oven Temperature Program: 100°-250°, 10°/min
Results: Major peak and one impurity

Peak	Retention Time (min.)	Normalized Retention Time	Normalized Peak Height
(1) Major	5.2	1.00	100.00
(2) Minor	6.6	1.26	1.38

System 2:

Instrument: Bendix 2500
Column: 3% OV-1 on Chromosorb W (HP), 1.8 m x 4 mm I.D.
Detector: Flame Ionization
Oven Temperature Program: 2 min. at 100°C, then
100°-250°C at 10°C/min.
Results: Major peak and three impurities

Peak	Retention Time (min.)	Normalized Retention Time	Normalized Peak Height
Minor	4.6	0.56	0.08
Major	8.2	1.00	100.00
Minor	10.1	1.24	1.80
Minor	11.1	1.35	0.03

E. SPECTRAL DATA

	Literature (Sadtler Standard Spectra)
1. Infrared Instrument: Beckman IR-12 Cell: 0.5% KBr pellet Results: See Figure 5	Consistent
2. Ultraviolet/Visible Instrument: Cary 118 ε max^{300} = (3.2 ± 0.2(δ)) x 10^3 ε max^{223} = (2.3 ± 0.1(δ)) x 10^4 No maxima between 350 and 800 nm (visible region) at 1.2 mg/ml Solvent: 95% Ethanol	Calculated from graph given in literature spectrum ε max^{300} = 3.18 x 10^3 ε max$^{223.5}$ = 2.16 x 10^4 Solvent: Methanol
3. Nuclear Magnetic Resonance Instrument: Varian HA-100 Solvent: Methanol-d_4 with internal TMS (See Figure 6) (a) 4.67δ, (b) 6.53-7.07δ, (c) 7.08-7.60δ Integration Ratios: (a) 1.56, (b) 4.06, (c) 4.94	Consistent

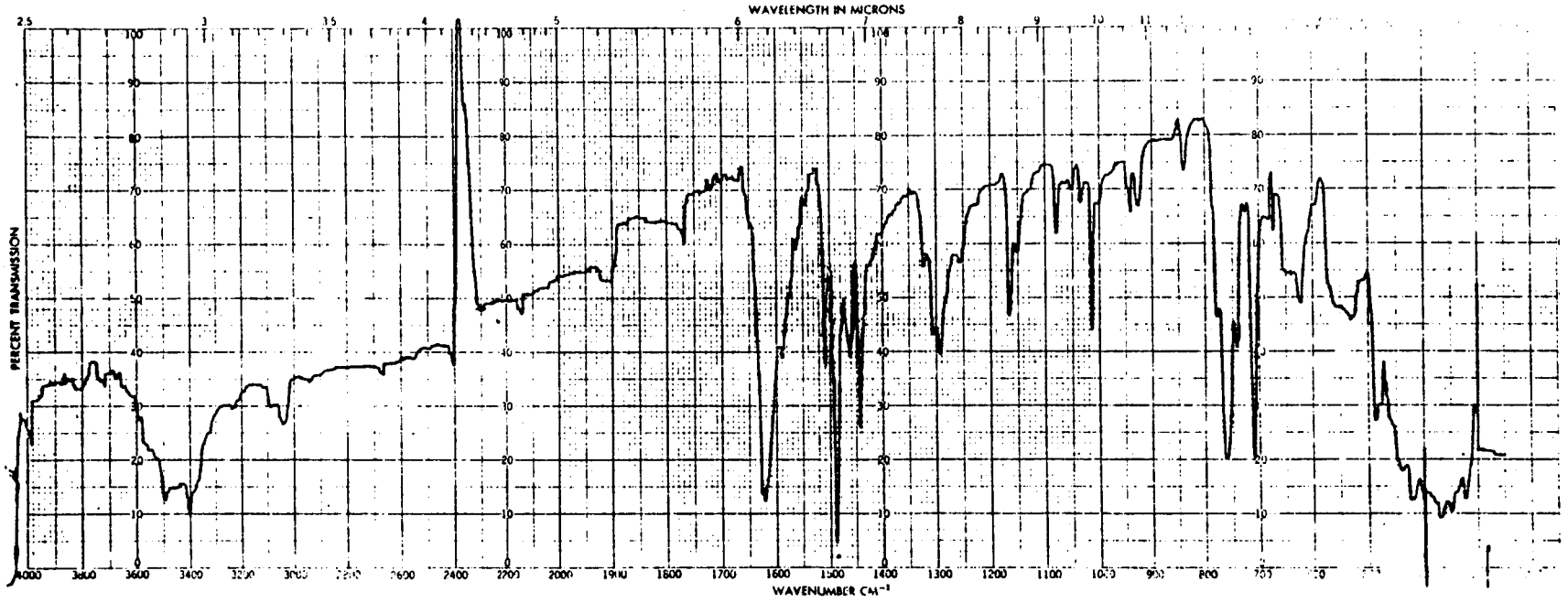

Figure 5. Infrared Absorption Spectrum of 2-Biphenylamine (Lot No. 081547)

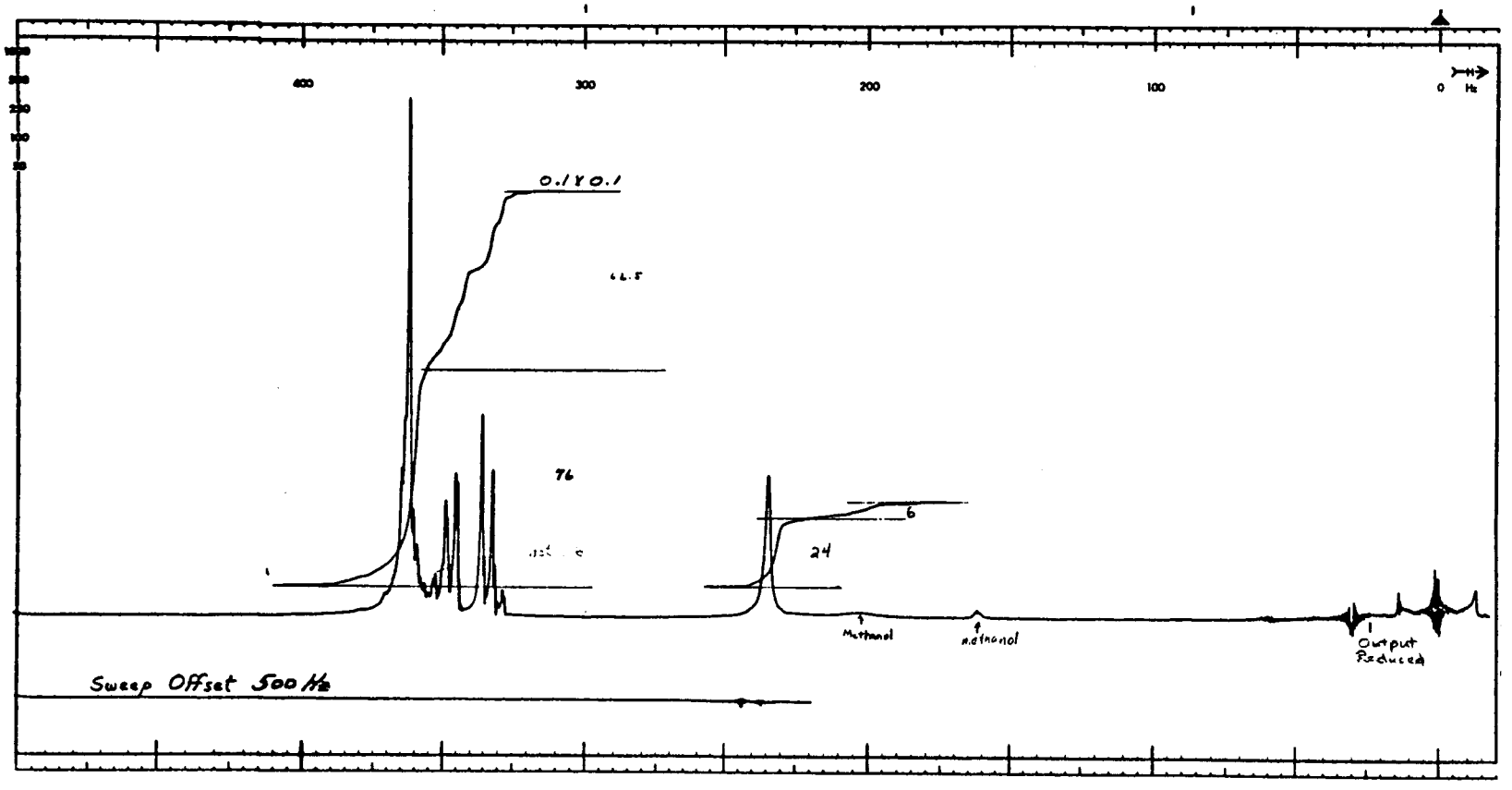

Figure 6. Nuclear Magnetic Resonance Spectrum of 2-Biphenylamine (Lot No. 081547)

APPENDIX F

ANALYSIS OF TECHNICAL-GRADE 2-BIPHENYLAMINE (LOT NO. CP121175) MIDWEST RESEARCH INSTITUTE

APPENDIX F

A. ELEMENTAL ANALYSIS

Element	C	H	N
Theory	85.17	6.55	8.28
Determined	85.06	6.65	8.34
	85.15	6.58	8.28

B. WATER ANALYSIS

(Karl Fisher)

0.53% ± 0.04 (δ)%

C. TITRATION

Nonaqueous titration of amine group with perchloric acid 97.14% ± 0.08 (δ)%.

D. MELTING POINT

Determined	Literature (Finzi and Leandri, 1950)
44°-51°C (visual capillary)	45°C

E. THIN-LAYER CHROMATOGRAPHY

Plates: Silica Gel 60F-254
Amount Spotted: 100 and 300 μg
Ref. Standard: Aniline
Visualization: Ultraviolet (254 and 366 nm)

System 1: Chloroform

R_f: 0.42 (major)
0.24 (trace)

R_{st}: 1.75, 1.00

System 2: Ethyl acetate

R_f: 0.88 (major)
0.78 (trace)

R_{st}: 1.16, 1.03

F. VAPOR-PHASE CHROMATOGRAPHY

System 1:

Instrument: Tracor MT-220
Column: 3% OV-1 on 80/100 Supelcoport, 1.8 m x 4 mm I.D.
Detector: Flame ionization
Oven Temperature Program: 100°C, 3 min; 100° to 250°C at 10°C/min.
Results: One homogenous peak (retention time 8.85 min)

System 2:

Instrument: Bendix 2500
Column: 3% OV-225 on 80/100 Chromosorb W (HP), 1.8 m x 4 mm I.D., glass
Detector: Flame ionization
Inlet temperature: 225°C
Detector temperature: 250°C
Oven Temperature Program: 3 min. at 100°C, then 100°-225°C at 10°C/min.
Results: major peak and six impurities

Peak	Retention Time (min.)	Retention Time (Relative to 2-Biphenlamine)	Area (Relative to 2-Biphenylamine)
1	2.6	0.25	0.07
2	10.6	1.00	100.00
3	11.2	1.10	0.09
4	12.9	1.26	0.03
5	14.2	1.39	0.05
6	14.6	1.43	0.9
7	15.1	1.48	0.02

Peak No. 6 was enhanced when 4-biphenylamine was added to the sample. This peak was quantitated against standard solutions of 4-biphenylamine using the same instrumental conditions as above except that the oven temperature program used was 175°C, isothermal. 4-Biphenylamine was found to be present at a concentration of 1.2%.

G. VAPOR-PHASE CHROMATOGRAPHY/MASS SPECTROMETRY

Instrument: Varian MAT CH4B mass spectrometer interfaced via a Watson-Biemann helium separator to a Tracor MT 2000 MF vapor-phase chromatograph. Data processed by a Varian 620/i computer.
Inlet temperature: 225°C
Column: 3% OV-225 on 80/100 Supelcoport, 1.8 m x 2 mm I.D. glass
Oven temperature program: 180°C, isothermal

Under these conditions, 4-biphenylamine had a retention time of 7.1 minutes. When 2-biphenylamine was injected under the same conditions, the major peak had a retention time of 2.2 minutes, and a minor peak was observed with a retention time of 7.1 minutes. The mass spectra of both of these peaks appeared to be consistent with that of biphenylamine. (The mass spectra of the 2- and 4-biphenylamine isomers are not significantly different.) However, the major peak was still being eluted when the minor peak was eluted at 7.1 minutes A computer search for the masses 169, 170 characteristics of biphenylamine showed that these masses decreased after the major peak was eluted and increased again under the peak at 7.1 minutes.

Conclusion: 4-Biphenylamine is present in the sample.

H. SPECTRAL DATA

Midwest Analysis	Literature
(1) Infrared	
Instrument: Beckman IR-12 Cell: Melt between NaCl Results: See Figure 7	Consistent with Sadtler Standard Spectra
(2) Ultraviolet/Visible	
Instrument: Cary 118	

λ max(nm)	$\varepsilon \times 10^{-3}$	λ max(nm)	$\varepsilon \times 10^{-3}$
300	3.13 ± 0.02 (δ)	300	3.18
250 (δ)	5.6 ± 0.1 (δ)	223.5	21.6
223	21.3 ± 0.3 (δ)		

Solvent: Methanol No maxima between 350 and 800 nm (visible region) at 1.1 mg/ml	Solvent; Methanol Calculated from graph given in literature (Sadtler Standard Spectra)
(3) Nuclear Magnetic Resonance	
Instrument: Varian HA-100 Solvent; Methanol-d_4 with TMS internal standard See Figure 8	Consistent with Sadtler Standard Spectra

(a) HDO and NH_2 δ □ 4.81 ppm
(b) δ = 6.69 - 7.26 ppm
(c) δ □ 7.30 - 7.58 ppm
(d) Solvent δ = 3.31 ppm

Integration Ratios:

(a) HDO and NH_2
(b) 4.20
(c) 4.80
(d) Solvent

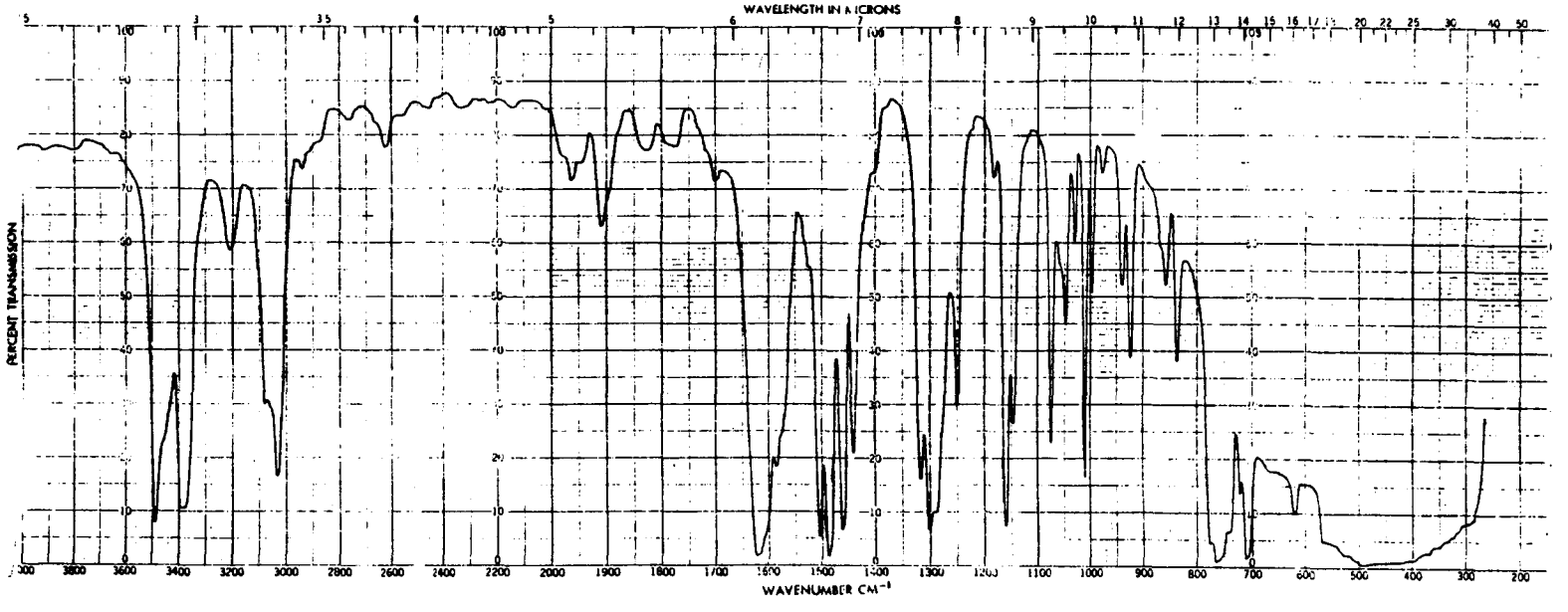

Figure 7. Infrared Absorption Spectrum of 2-Biphenylamine (Lot No. CP121175)

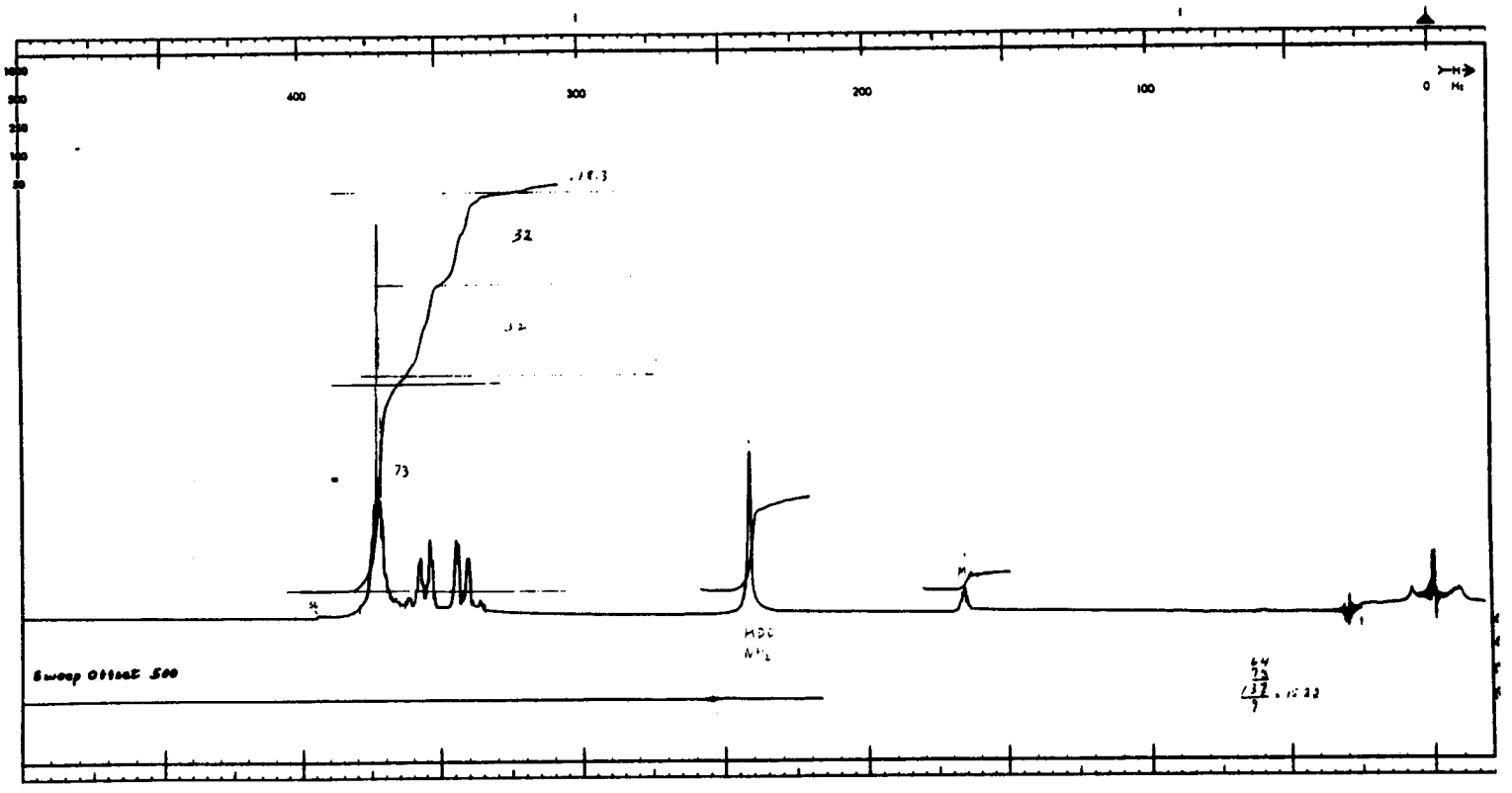

Figure 8. Nuclear Magnetic Resonance Spectrum of 2-Biphenylamine (Lot No. CP121175)

APPENDIX G

ANALYSIS OF 2-BIPHENYLAMINE HYDROCHLORIDE
(LOT NO. MRI 9-9-75)
MIDWEST RESEARCH INSTITUTE

APPENDIX G

A. ELEMENTAL ANALYSIS (dried 56°C/4 mm, 48 hr)

Element	C	H	N	Cl
Theory	70.07	5.88	6.81	17.24
Determined	70.44	5.96	6.80	17.08
	70.40	5.98	6.88	17.52

B. WATER ANALYSIS

(Karl Fisher) 3.3 ± 0.1 (δ)%

C. NONAQUEOUS TITRATION OF AMINE GROUP IN PRESENCE OF MERCURIC ACETATE

98.1 ± 0.2 (δ)% (dried 56°C/4 mm, 48 hr)

D. MELTING POINT

Determined	Literature Values
m.p. 140°C (begins to sublime); 175°C (complete sublimation); visual, sealed evacuated capillary	m.p. 201°C (Coffin and Robbins, 1965)

E. THIN LAYER CHROMATOGRAPHY

Plates: Silica gel G, F254
Amount Spotted: 100 and 300 μg
Ref. Standard: Aniline
Visualization: Ultraviolet, 254 and 366 nm

System 1: Chloroform, 100%
R_f: 0.44, 0.27 (trace)
R_{st}: 2.1, 1.3

System 2: Ethyl acetate, 100%
R_f: 0.84, 0.78 (trace)
R_{st}: 1.1, 1.0

F. VAPOR-PHASE CHROMATOGRAPHY

Instrument: Tracor MT-220
Column: 3% Dexsil 400, 1.6 m x 2 mm I.D.
Detector: Flame ionization
Oven Temperature Program: 5 min hold at 100°C, then 100° to 250° at 10°C/min
Results: Major peak and one impurity

Peak	Retention Time (min.)	Retention Time (Relative to 2-Biphenylamine Hydrochloride)	Area (Relative to 2-Biphenylamine Hydrochloride)
1	9.4	1.0	100
2	12.6	1.3	0.05

APPENDIX G

G. HIGH PRESSURE LIQUID CHROMATOGRAPHY

Instrument: ALC 202 with Model 660 Solvent Programmer
Column: C_{18} μ Bondapak
Detector: UV-254 nm
Solvent: 50 to 100% CH_3CN in H_2O
Program: 6
Program Time: 15 min
Flow: 1 ml/min
Results: Major peak and one minor peak

Peak	Retention Time (min.)	Normalized Retention Time	Relative Area
minor	8.9	0.92	0.62
major	9.7	1.00	100.00

H. SPECTRAL DATA

1. Infrared
   Instrument: Beckman IR-12
   Cell: 1% KBr pellet
   Results: See Figure 9.

   No literature reference found for the hydrochloride salt. Spectrum consistent with that of a 2-substituted aromatic amine hydrochloride.

2. Ultraviolet/Visible
   Instrument: Cary 118

   Literature Values (Sadtler Standard Spectra)

   No literature spectrum found for hydrochloride. Values reported are calculated from a graph of the spectrum of the free base given in the literature.

λ max (nm)	$\varepsilon \times 10^{-3}$	λ max (nm)	$\varepsilon \times 10^{-3}$
300	0.86 ± 0.07	300	3.18
222.5	21.0 ± 0.2	223.5	21.6

   No absorbance between 350 and 800 nm (visible range) at a concentration of 1 mg/ml.

   Solvent: Methanol

   Solvent: Methanol

3. Nuclear Magnetic Resonance
   Instrument: Varian HA-100
   Solvent: CD_3OD with internal tetramethylsilane

   No literature spectrum found.

   Assignments (See Figure 10)
   (a) m, δ 7.46 - 7.81 ppm
   (b) s, δ 5.49 ppm, HDO and NH_2
   (c) s, δ 3.36 ppm, CH_3 from CH_3OH in sample
   Integration Ratios:

   (a) 9.00
   Methanol content calculated from relative areas of (a) and (c): 0.6%

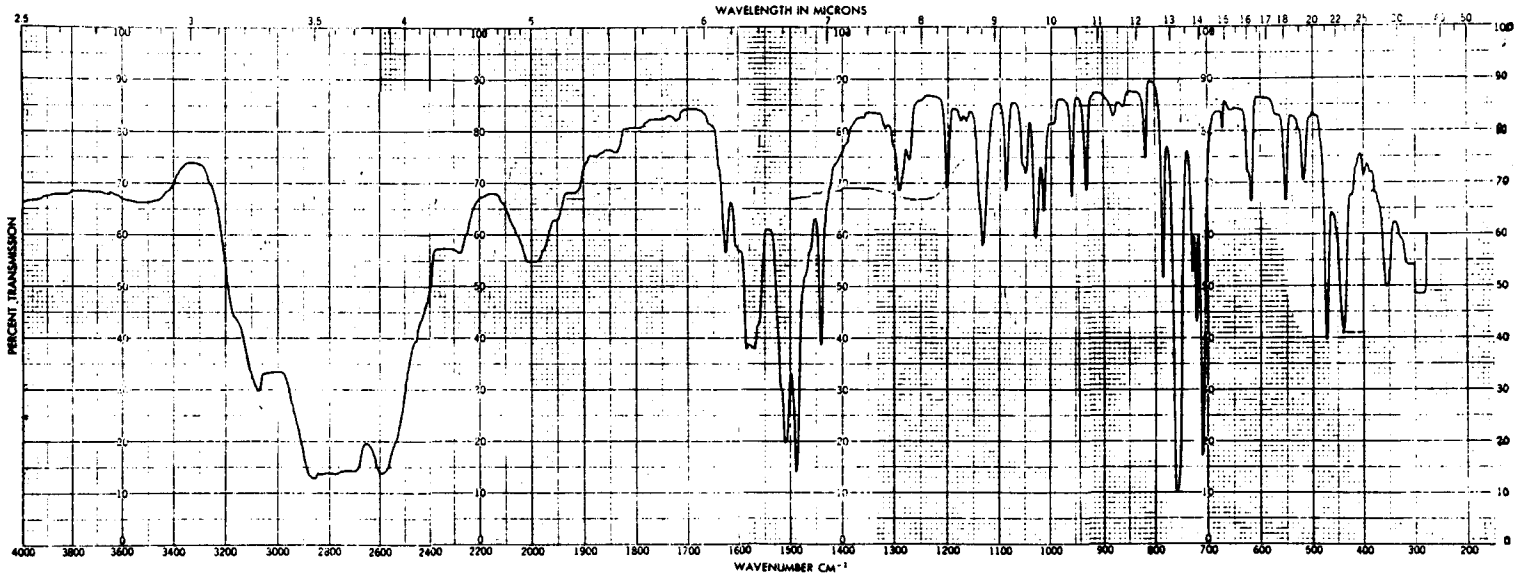

Figure 9. Infrared Absorption Spectrum of 2-Biphenylamine Hydrochloride (Lot No. MRI 9-9-75)

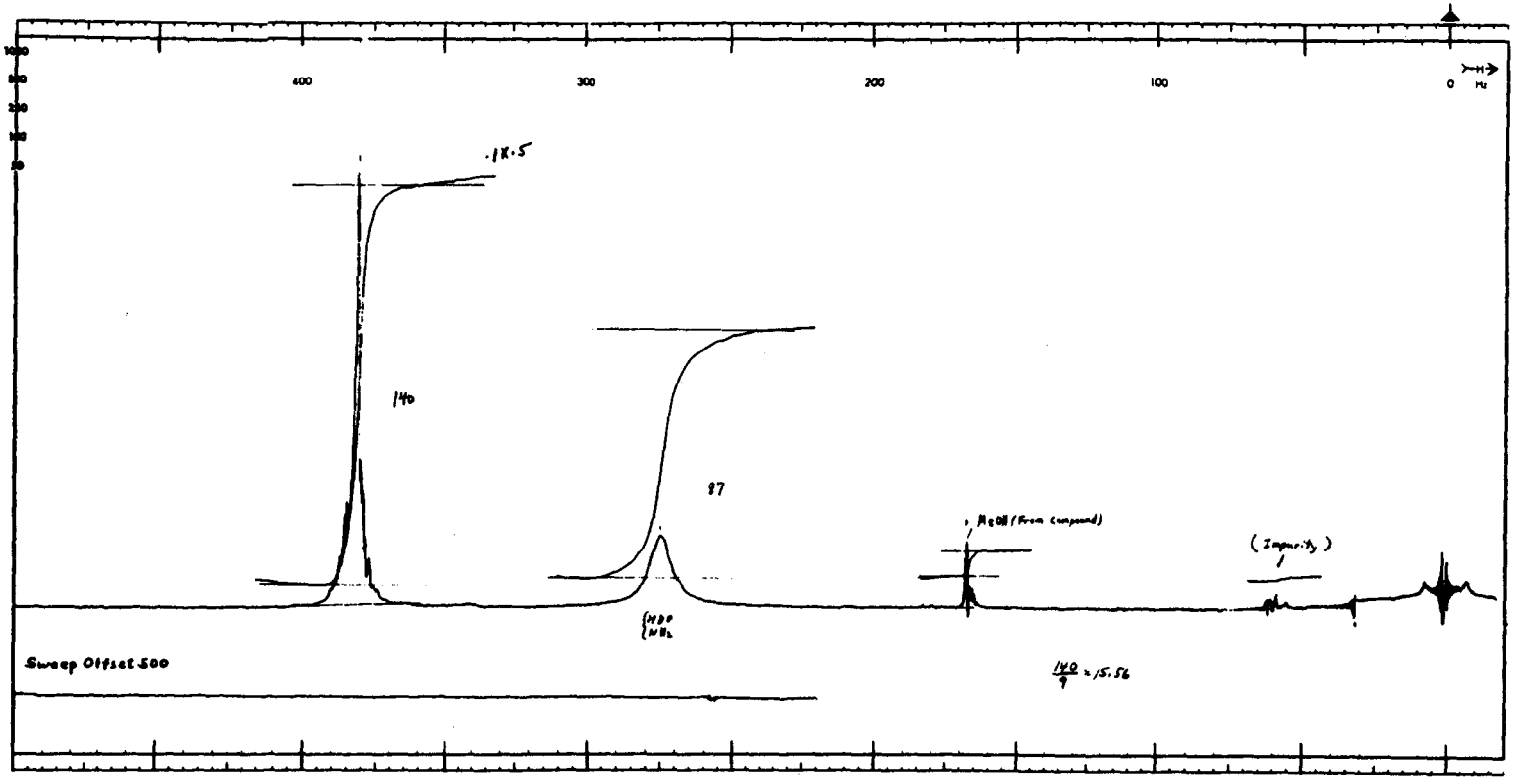

Figure 10. Nuclear Magnetic Resonance Spectrum of 2-Biphenylamine Hydrochloride (Lot No. MRI 9-9-75)

APPENDIX G

I. DETERMINATION OF 4-BIPHENYLAMINE CONTAMINANT LEVEL

1. PROCEDURE

A weighed amount of Lot No. MRI 9-9-75 was dissolved in methanol in a small septum vial to make a solution of 10.47 $\mu g/\mu l$ concentration. A 4-biphenylamine standard solution was likewise made up at 0.024 $\mu g/\mu l$. These solutions were quantitatively compared by vapor-phase chromatography.

2. SYSTEM

Instrument: Tracor MT-220
Column: 3% OV-225 on Supelcoport, 80/100, 100, 1.8 m x 4 mm I.D., glass
Detection: Flame ionization
Inlet temperature: 200°C
Detector temperature: 270°C
Oven temperature: 175°C, isothermal

3. RESULTS

The 4-biphenylamine content of this lot of 2-biphenylamine hydrochloride was found to be 0.198% ± 0.017%.

APPENDIX H

PREPARATION OF 2-BIPHENYLAMINE HYDROCHLORIDE AND ANALYSIS FOR CONCENTRATION OF 4-BIPHENYLAMINE MIDWEST RESEARCH INSTITUTE

APPENDIX H

A. PREPARATION OF 2-BIPHENYLAMINE HYDROCHLORIDE FROM TECHNICAL-GRADE 2-BIPHENYLAMINE

2-Biphenylamine (187.5 g, 1.11 mole) was dissolved in 1.5 liters of absolute ether in a 2-liter beaker. Concentrated hydrochloric acid (37.5% HCl sp. gr. [15/15] = 1.19; 180 ml) was added over a period of 5 minutes to the ether solution with constant stirring (glass rod). Care was taken not to add the acid too rapidly, since some heat is liberated during the reaction. As the acid was added, the hydrochloride salt precipitated from the reaction mixture.

When the acid addition was complete, the mixture was suction filtered through a sintered glass Buchner funnel. The precipitate was thoroughly washed with ether, and the filtrate washings were rejected. The washed precipitate was briefly air dried. This procedure was repeated on successive portions of 2-biphenylamine, until 3,000 g of the hydrochloride salt had been prepared.

The crude salt was purifed by batch reprecipitation from methanol. Anhydrous ether was slowly added to a saturated solution of the salt in 400 ml of methanol until no further precipitate formed with additional ether (required approximately 3 liters of ether). The reprecipitated salt was separated by suction filtration and air dried for 5 minutes. It was then transferred to an evacuated (water aspirator) dessicator and dried over anhydrous calcium sulfate. Total yield of dried, reprecipitated salt: 2,500 g, 83.3% recovery.

In all of the above operations, the neutral 2-biphenylamine and the hydrochloride salt were protected from bright or direct light as much as possible.

B. ANALYSIS FOR 4-BIPHENYLAMINE HYDROCHLORIDE

1. Procedure

A 441.4-mg sample of the 2-biphenylamine hydrochloride was weighed into a small septum vial and dissolved in 5.0 ml methanol. The solution was colorless. Standard solutions were prepared from a 0.023% 4-biphenylamine standard, corresponding to a concentration of 0.023% impurity in the 2-biphenylamine hydrochloride. Sample and standard solutions were analyzed by vapor-phase chromatography.

2. System

Instrument: Bendix 2500 with Hewlett-Packard 3380A Integrator
Column: 3% OV-225 on Chromosorb W (HP), 80/100 mesh, glass, 1.8 m x 4 mm I.D.
Oven temperature: 175°C, isothermal
Inlet temperature: 200°C
Flame ionization detector temperature: 270°C
2-Biphenylamine retention time: 3.2 min.
4-Biphenylamine retention time: 8.3 min.
Carrier gas: Nitrogen; flow rate, 40 cc/min.

3. Results

Batch No. WN-1-61-RC1: 4-Biphenylamine hydrochloride content found: 0.014 ± 0.003%

Batch No. WN-1-61-R2: 4-Biphenylamine hydrochloride content found: 0.023 ± 0.003%

Batch No. WN-1-61-R3: 4-Biphenylamine hydrochloride content found: 0.049 ± 0.003%

Batch No. WN-1-61-R4: 4-Biphenylamine hydrochloride content found: 0.006% (after 3rd crystallization)

APPENDIX I

ANALYSIS OF FORMULATED DIETS FOR STABILITY OF TECHNICAL-GRADE 2-BIPHENYLAMINE MIDWEST RESEARCH INSTITUTE

APPENDIX I

A. MIXING AND STORAGE

2-Biphenylamine (0.3411 g) and Wayne Lab-Blox® Rodent Feed (33.7600 g) were mixed in a mortar. Samples of the mixture were removed and stored for 2 weeks at -20°, 5°, 25°, and 45°C, respectively.

B. EXTRACTION AND ANALYSIS

Five-gram samples of the chemical/feed mixtures were mixed with 50 ml of methanol in an ultrasonic vibratory bath for 30 seconds and then triturated for 1 minute using a Polytron® high-speed blender. The resulting mixture was centrifuged, and the methanolic supernatant was decanted into a 100-ml volumetric flask. This extraction procedure was repeated on the feed residue, after which the total supernatant solution in the volumetric flask was made up to volume with additional methanol. This solution was then analyzed by the vapor-phase chromatographic method outlined below:

Instrument: Tracor MT-220
Column: 3% OV-1 on Supelcoport, 80/100 mesh, 1.8 m x 4 mm I. D., glass
Detection: Flame ionization
Temperatures: Inlet - 250°C
Oven - 145°C isothermal
Detector - 275°C
Retention time of compound: 2.2 min.

C. RESULTS

Sample (°C)	Average Percent *(a)*
-20	0.79 ± 0.16
5	1.02 ± 0.16
25	1.05 ± 0.16
45	0.97 ± 0.16

(a) Corrected for a spiked recovery yield of 95.8% ± 0.2%; theoretical yield, 0.99%.

There was no significant difference between the samples stored at the various temperatures (except for the -20° sample, which would be expected to be the most stable of all the samples).

D. CONCLUSION

2-Biphenylamine mixed with feed is stable for 2 weeks at temperatures up to 45°C.

APPENDIX J

ANALYSIS OF FORMULATED DIETS FOR STABILITY OF 2-BIPHENYLAMINE HYDROCHLORIDE MIDWEST RESEARCH INSTITUTE

APPENDIX J

A. SAMPLE PREPARATION AND STORAGE

Wayne Lab-Blox® Rodent Feed samples (5 g) were weighed and transferred into 200-ml glass centrifuge bottles. To prepare the 10,000 ppm mixtures, 50 mg of 2-biphenylamine hydrochloride was weighed and transferred into each centrifuge bottle; 25 mg of the chemical was added to the feed to make the 5,000 ppm mixtures. The dosed feed samples were thoroughly shaken manually and on a vortex mixer for 30 seconds. Duplicate samples were then stored at -20°, 5°, 25°, and 45°C, respectively, for both 1 week and 2 weeks. Control spikes (zero-time samples) were prepared in the same manner but not stored.

B. EXTRACTION AND ANALYSIS

Each sample was triturated with 50 ml of absolute methanol for 30 seconds using a Brinkmann Polytron® high-speed blender. The mixture was then placed in an ultrasonic vibratory bath for 1 minute and centrifuged for 10 minutes. The methanolic supernatant solution was decanted into a 100-ml volumetric flask, and the feed residue was re-extracted in the same manner with 50 ml of fresh methanol. The two supernatants were combined and brought to volume with additional methanol. This resulting solution was analyzed by the vapor-phase chromatographic system described below:

Instrument: Bendix 2500 with Hewlett-Packard Model 3308A automatic integrator
Column: 3% Dexsil 400 on 80/100 mesh Chromosorb W (AW) DMCS, 1.8 m x 2 mm I.D., glass
Detection: Flame ionization
Temperatures: Inlet - 225°C
Oven - 155°C isothermal
Detector - 285°C
Carrier gas: Nitrogen; flow rate, 40 cc/min.
Retention time of nominal compound: 2.5 min.
Reference standard: 2-Biphenylamine hydrochloride

C. RESULTS

Storage Temperatures (°C)	Average Percent of Chemical Found in Chemical/Vehicle Mixture *(a)*	
	7 Days	14 Days
5,000 ppm Dose Level		
-20	0.46 ± 0.04	0.50 ± 0.05
5	0.52 ± 0.05	0.50 ± 0.05
25	0.49 ± 0.05	0.49 ± 0.04
45	0.36 ± 0.03	0.36 ± 0.04
10,000 ppm Dose Level		
-20	0.98 ± 0.08	1.01 ± 0.08
5	1.01 ± 0.08	1.03 ± 0.06
25	1.01 ± 0.08	0.89 ± 0.05
45	0.87 ± 0.07	0.80 ± 0.05

(a) Corrected for a spike recovery yield of 97% ± 6%. The error figures are standard deviations propagated by standard numerical methods in the correction for spike recovery yield.

D. CONCLUSION

2-Biphenylamine hydrochloride is stable when mixed with stock rodent feed at 5,000 and 10,000 ppm and stored for one week at -20°, 5°, and 25°C, respectively. Significantly less than 100% of the original nominal dose was determined for all samples stored at 45° and for 10,000 ppm samples stored at 25° for 2 weeks.

Since the amounts of chemical determined were the same (within the limits of error) for 1 and 2 weeks at 45° for the 5,000-ppm mixture, and for 2 weeks at 25° and 1 and 2 weeks at 45° for the 10,000-ppm mixture, it is possible that these low determinations represent a lack of extractability of this chemical from feed (which becomes apparent only at higher temperatures, longer storage times, and higher dose levels), rather than indicating an actual chemical transformation (i.e., true instability).

APPENDIX K

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF 2-BIPHENYLAMINE HYDROCHLORIDE MASON RESEARCH INSTITUTE

Duplicate samples of 2 g each were extracted with 50 ml of methanol. The supernatant solutions were analyzed by VPC-FID at 165°on a 6 ft. x .25 in. x 2 mm I.D. glass column packed with 3% SP2250 on 100/120 mesh Supelcoport (see Table K1). Recoveries were determined by direct comparison with a calibration curve prepared and analyzed in the same manner from feed spiked with test compound at six levels.

Table K1. ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF 2-BIPHENYLAMINE HYDROCHLORIDE

Date Mixed	Date Used (Week of)	Concentration of 2-Biphenylamine Hydrochloride in Feed for Target Concentration of: 1,000 ppm	3,000 ppm
6/19/78	6/21/78	950	2,900
9/18/78	9/20/78	920	2,600
10/30/78	10/31/78	970	2,900
1/22/79	1/24/79	950	2,600
2/12/79	2/14/79	970	3,100
5/7/79	5/9/79	860	2,750
7/9/79	7/11/79	950	2,800
8/27/79	8/29/79	925	2,900
10/8/79	10/10/79	925	2,950
11/19/79	11/21/79	920	2,830
2/15/80	2/17/80	1,000	
2/20/80	2/22/80		2,900
Mean (ppm)		940	2,839
Standard Dev.		37	148
Coefficient of Variation (%)		3.9	5.2
Range (ppm)		860-1,000	2,600-3,100
Number of Samples		11	11

APPENDIX L

SINGLE-DOSE ACUTE TOXICITY WITH TECHNICAL-GRADE 2-BIPHENYLAMINE IN F344/N RATS AND B6C3F1/N MICE

TABLE L1. SINGLE-DOSE ACUTE TOXICITY WITH TECHNICAL-GRADE 2-BIPHENYLAMINE IN F344/N RATS AND B6C3F1/N MICE

	Dose (g/kg)	Survival	
		Male	Female
Rats			
	0.001	2/2	2/2
	0.01	2/2	2/2
	0.1	2/2	2/2
	1.0	2/2	2/2
	10.0	0/2 *(a)*	0/2 *(b)*
Mice			
	0.001	2/2	2/2
	0.01	2/2	2/2
	0.1	2/2	2/2
	1.0	1/2 *(c)*	2/2
	10.0	0/2 *(d)*	0/2 *(d)*

(a) Deaths occurred on days 2 and 4.
(b) Deaths occurred on days 2 and 3.
(c) Death occurred on day 6
(d) Both animals died on day 2.

TABLE L2. SURVIVAL, WEIGHT GAIN, AND CLINICAL OBSERVATIONS FOR RATS AND MICE ADMINISTERED SINGLE DOSES OF TECHNICAL-GRADE 2-BIPHENYLAMINE IN CORN OIL BY GAVAGE

Dose (mg/kg)	Sex	Animal No.	Weight (grams)			Disposition	Date	Clinical Observations
			Initial	Day 7	Final			
Rats								
0.001	M	1	106	133	160	Killed	4/9	Slight enlargement of lymphatics noted at necropsy
	M	2	101	140	178	Killed	4/9	
	F	1	92	114	126	Killed	4/9	
	F	2	80	108	125	Killed	4/9	
0.01	M	1	96	140	169	Killed	4/9	General lymphatic enlargement: slight thickening of duodenal mucosa noted at necropsy
	M	2	105	165	193	Killed	4/9	
	F	1	90	114	130	Killed	4/9	
	F	2	76	104	124	Killed	4/9	
0.1	M	1	107	130	162	Killed	4/9	Lethargy and diarrhea during first 24 hrs; general lymphatic enlargement
	M	2	90	120	162	Killed	4/9	
	F	1	82	110	126	Killed	4/9	
	F	2	94	120	136	Killed	4/9	
1.0	M	1	106	137	175	Killed	4/9	Lethargy during first 24 hrs; general lymphatic enlargement; thickened duodenal mucosa observed at necropsy
	M	2	100	140	176	Killed	4/9	
	F	1	77	90	114	Killed	4/9	
	F	2	90	102	126	Killed	4/9	
10.0	M	1	100	—	100	Died	3/29	Hyperactivity; then postration and shallow breathing following administration; apparent regurgitation of gavaged material at death; red nasal conchae and enlarged lymphatics observed at necropsy
	M	2	130	—	126	Died	3/27	
	F	1	90	—	88	Died	3/28	
	F	2	100	—	96	Died	3/27	

TABLE L2. SURVIVAL, WEIGHT GAIN, AND CLINICAL OBSERVATIONS FOR RATS AND MICE ADMINISTERED SINGLE DOSES OF TECHNICAL-GRADE 2-BIPHENYLAMINE IN CORN OIL BY GAVAGE (Continued)

Dose (mg/kg)	Sex	Animal No.	Weight (grams)			Disposition	Date	Clinical Observations
			Initial	Day 7	Final			
Mice								
0.001	M	1	19	26	22	Killed	4/9	Enlarged Peyer's Patches observed at necropsy
	M	2	21	24	23	Killed	4/9	
	F	1	20	22	21	Killed	4/9	
	F	2	17	18	17	Killed	4/9	
0.01	M	1	24	20	22	Killed	4/9	Enlarged Peyer's Patches; slight opacity in central area (lens) of eyes observed at necropsy
	M	2	23	25	27	Killed	4/9	
	F	1	18	16	17	Killed	4/9	
	F	2	16	18	19	Killed	4/9	
0.1	M	1	22	26	20	Killed	4/9	Enlarged Peyer's Patches; slight opacity in central area (lens) of eyes observed at necropsy
	M	2	19	22	21	Killed	4/9	
	F	2	20	20	19	Killed	4/9	
	F	1	18	20	20	Killed	4/9	
1.0	M	1	25	—	22	Died	4/1	Gavage accident
	M	2	20	22	22	Killed	4/9	Enlarged Peyer's Patches and lymph nodes. Lethargy following administration
	F	1	16	18	18	Killed	4/9	
	F	2	20	18	18	Killed	4/9	
10.0	M	1	24	—	22	Died	3/27	Dark intestinal contents, reddened nasal conchae, enlarged lymphatics; hyperactivity then prostration and shallow breathing following administration
	M	2	24	—	25	Died	3/27	
	F	1	20	—	20	Died	3/27	
	F	2	19	—	19	Died	3/27	

(a) Study started on 3/26/75 and completed on 4/9/75

APPENDIX M

FEED CONSUMPTION BY RATS AND MICE RECEIVING 2-BIPHENYLAMINE HYDROCHLORIDE

TABLE M1. FEED CONSUMPTION BY MALE RATS RECEIVING 2-BIPHENYLAMINE HYDROCHLORIDE

Week	Control	Low		High	
	Grams Feed/ Day*(a)*	Grams Feed/ Day*(a)*	Low/ Control *(b)*	Grams Feed/ Day*(a)*	High/ Control *(b)*
4	14.9	13.7	0.9	13.6	0.9
8	16.7	14.3	0.9	15.7	0.9
11	20.7	20.6	1.0	20.3	1.0
16	18.6	20.6	1.1	18.7	1.0
20	18.7	23.1	1.2	19.7	1.1
24	25.6	26.1	1.0	27.3	1.1
28	22.0	20.4	0.9	18.9	0.9
32	20.4	17.7	0.9	16.6	0.8
36	24.6	21.9	0.9	20.7	0.8
40	23.1	22.6	1.0	21.1	0.9
44	26.4	20.9	0.8	20.4	0.8
48	16.4	18.1	1.1	17.4	1.1
52	20.1	18.3	0.9	17.1	0.9
56	23.1	20.6	0.9	20.9	0.9
60	18.7	18.9	1.0	17.9	1.0
64	26.6	20.6	0.8	19.1	0.7
68	20.9	20.0	1.0	20.6	1.0
72	20.1	23.6	1.2	21.4	1.1
76	22.1	20.4	0.9	19.6	0.9
80	26.3	24.4	0.9	24.6	0.9
84	23.6	22.3	0.9	21.1	0.9
88	21.9	21.3	1.0	19.3	0.9
92	24.6	25.6	1.0	23.1	0.9
96	27.4	24.1	0.9	31.1	1.1
100	26.9	24.3	0.9	24.6	0.9
104	29.1	25.4	0.9	22.1	0.8
Mean	22.3	21.1	1.0	20.5	0.9
SD *(c)*	3.7	3.1	0.1	3.6	0.1
CV *(d)*	16.6	14.7	10.0	17.6	11.1

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

TABLE M2. FEED CONSUMPTION BY FEMALE RATS RECEIVING 2-BIPHENYLAMINE HYDROCHLORIDE

	Control	Low		High	
Week	Grams Feed/ Day*(a)*	Grams Feed/ Day*(a)*	Low/ Control *(b)*	Grams Feed/ Day*(a)*	High/ Control *(b)*
4	12.9	14.9	1.2	8.6	0.7
8	8.6	10.4	1.2	12.9	1.5
11	14.6	15.4	1.1	12.4	0.9
16	15.0	15.4	1.0	12.0	0.8
20	18.9	17.4	0.9	14.1	0.8
24	14.9	14.9	1.0	13.1	0.9
28	17.3	15.9	0.9	13.6	0.8
32	18.1	17.6	1.0	12.7	0.7
36	21.7	20.9	1.0	16.1	0.7
40	23.0	21.9	1.0	15.6	0.7
44	26.0	22.7	0.9	14.7	0.6
48	16.4	22.9	1.4	14.9	0.9
52	18.4	16.3	0.9	15.6	0.8
56	22.1	18.4	0.8	16.1	0.7
60	17.1	16.7	1.0	15.3	0.9
64	19.3	17.6	0.9	16.0	0.8
68	18.9	16.6	0.9	15.9	0.8
72	19.1	16.1	0.8	13.4	0.7
76	18.6	15.7	0.8	14.0	0.8
80	18.0	17.7	1.0	15.9	0.9
84	17.9	15.9	0.9	14.9	0.8
88	16.9	16.0	0.9	14.7	0.9
92	19.4	17.6	0.9	15.1	0.8
96	22.1	22.4	1.0	19.1	0.9
100	26.0	23.3	0.9	19.4	0.7
104	19.4	18.0	0.9	18.1	0.9
Mean	18.5	17.6	1.0	14.8	0.8
SD *(c)*	3.8	3.1	0.1	2.3	0.2
CV *(d)*	20.5	17.6	10.0	15.5	25.0

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

TABLE M3. FEED CONSUMPTION BY MALE MICE RECEIVING 2-BIPHENYLAMINE HYDROCHLORIDE

	Control	Low		High	
Week	Grams Feed/ Day*(a)*	Grams Feed/ Day*(a)*	Low/ Control *(b)*	Grams Feed/ Day*(a)*	High/ Control *(b)*
4	8.3	7.6	0.9	7.0	0.8
8	7.7	7.6	1.0	7.6	1.0
11	7.6	6.9	0.9	6.7	0.9
17	6.4	6.0	0.9	6.6	1.0
20	6.7	7.1	1.1	6.3	0.9
24	8.1	7.9	1.0	7.6	0.9
28	7.6	7.1	0.9	7.9	1.0
32	7.1	8.4	1.2	7.4	1.0
36	8.1	8.3	1.0	7.3	0.9
40	8.0	7.6	0.9	7.3	0.9
44	8.0	7.4	0.9	8.0	1.0
48	7.3	6.7	0.9	7.3	1.0
52	5.7	6.3	1.1	6.1	1.1
56	6.0	6.6	1.1	5.9	1.0
60	7.0	7.3	1.0	7.4	1.1
63	8.3	7.3	0.9	7.9	0.9
68	6.6	6.9	1.0	6.9	1.0
73	8.3	9.3	1.1	9.4	1.1
76	8.3	7.1	0.9	9.6	1.2
80	7.3	6.9	0.9	7.1	1.0
84	15.3	8.1	0.5	14.3	0.9
89	7.6	8.1	1.1	9.1	1.2
93	7.1	7.3	1.0	7.4	1.0
96	7.6	7.6	1.0	8.6	1.1
100	7.1	8.1	1.1	8.4	1.2
Mean	7.7	7.4	1.0	7.8	1.0
SD *(c)*	1.7	0.7	0.1	1.7	0.1
CV (d)	22.1	9.5	10.0	21.8	10.0

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

TABLE M4. FEED CONSUMPTION BY FEMALE MICE RECEIVING 2-BIPHENYLAMINE HYDROCHLORIDE

Week	Control	Low		High	
	Grams Feed/ Day*(a)*	Grams Feed/ Day*(a)*	Low/ Control *(b)*	Grams Feed/ Day*(a)*	High/ Control *(b)*
4	9.0	7.6	0.8	10.9	1.2
8	8.6	8.3	1.0	8.6	1.0
11	7.0	7.1	1.0	7.1	1.0
17	7.7	6.9	0.9	6.9	0.9
20	8.1	7.3	0.9	7.7	0.9
24	9.1	7.1	0.8	7.9	0.9
28	8.9	8.1	0.9	8.6	1.0
32	8.7	7.7	0.9	7.0	0.8
36	9.4	7.0	0.7	7.9	0.8
40	9.1	8.7	1.0	8.6	0.9
44	8.4	7.4	0.9	8.0	0.9
48	11.3	7.9	0.7	7.9	0.7
52	7.7	7.4	1.0	8.0	1.0
56	7.1	7.7	1.1	6.9	1.0
60	7.7	7.6	1.0	8.0	1.0
63	8.1	7.6	0.9	7.9	1.0
68	8.3	7.6	0.9	8.3	1.0
73	8.9	8.9	1.0	9.0	1.0
76	9.3	8.4	0.9	9.0	1.0
80	8.1	7.4	0.9	8.1	1.0
84	8.4	7.9	0.9	7.9	0.9
89	9.3	9.9	1.1	6.9	0.7
92	8.9	7.6	0.9	9.1	1.0
96	9.0	8.4	0.9	9.4	1.0
100	9.1	8.3	0.9	10.1	1.1
Mean	8.6	7.8	0.9	8.2	1.0
SD *(c)*	0.9	0.7	0.1	1.0	0.1
CV *(d)*	10.5	9.0	11.1	12.2	10.0

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

☆U.S. GOVERNMENT PRINTING OFFICE: 1982-381-132:692

NIH Publication No. 83-1789
October 1982

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