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TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZOFURAN

(CAS NO. 271-89-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZOFURAN

(CAS NO. 271-89-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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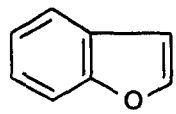

BENZOFURAN

CAS No. 271-89-6

C_8H_6O Molecular weight 118.1

Synonyms: Coumarone; cumarone

ABSTRACT

Benzofuran is used as an intermediate in the polymerization of coumarone-indene resins found in various corrosion-resistant coatings such as paints and varnishes, in water-resistant coatings for paper products and fabrics, and in adhesives approved for use in food containers. Toxicology and carcinogenesis studies were conducted by administering benzofuran (approximately 99% pure) in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 14 days, 13 weeks, or 2 years. Genetic toxicology tests were conducted in *Salmonella typhimurium*, mouse lymphoma cells, and Chinese hamster ovary (CHO) cells.

Fourteen-Day Studies: Benzofuran doses for groups of five rats ranged from 63 to 1,000 mg/kg and from 16 to 250 mg/kg for mice. All male and female rats that received 1,000 mg/kg and one female rat that received 500 mg/kg died before the end of the studies. The final mean body weights of male rats that received 250 or 500 mg/kg were 13% or 21% lower than that of controls; the final mean body weight of female rats that received 500 mg/kg was 10% lower than that of controls. Final mean body weights of chemically exposed and control mice were similar. No compound-related histologic lesions were found in rats or mice.

Thirteen-Week Studies: Doses for groups of 10 rats and groups of 10 mice ranged from 31 to 500 mg/kg. One female rat that received 500 mg/kg and one that received 250 mg/kg died before the end of the study. Final mean body weights of male rats that received 125, 250, or 500 mg/kg were 11%, 17%, or 27% lower than that of vehicle controls; the final mean body weight of female rats that received 500 mg/kg was 11% lower than that of vehicle controls. Histologic lesions observed in chemically exposed rats included minimal hepatocellular necrosis, increased severity of nephropathy, and cytoplasmic vacuolization of the adrenal cortex.

Seven male and three female mice that received 500 mg/kg and one male mouse that received 250 mg/kg died before the end of the 13-week studies. The final mean body weight of mice that received 500 mg/kg was 13% lower than that of vehicle controls. Nephrosis was observed in male mice that received 250 mg/kg.

Based on reduced mean body weights, increased severity of nephropathy, and hepatocellular necrosis, benzofuran doses selected for the 2-year studies in rats were 30 or 60 mg/kg for males and 60 or 120 mg/kg for females. Based on increased mortality and nephrosis in male mice, doses selected for the 2-year studies in mice were 60 or 120 mg/kg for males and 120 or 240 mg/kg for females.

Body Weights and Survival in the Two-Year Studies: Mean body weights of high dose rats and dosed male mice were 4%-11% lower than those of vehicle controls. Mean body weights of chemically exposed female mice were 8%-35% lower than those of vehicle controls. The survival of chemically exposed male rats was reduced after week 92 (survival at week 89: vehicle control, 47/50; low dose, 39/50; high dose, 38/50; final survival: vehicle control, 33/50; low dose, 12/50; high dose, 18/50).

Survival of chemically exposed female rats and male mice was similar to that of vehicle controls after 2 years (female rats: 27/50; 23/50; 25/50; male mice: 33/50; 20/50; 28/50). Deaths of 10 low dose male mice at weeks 20-21 were caused by a dosing error; these animals were not included in survival and tumor analyses. Survival of chemically exposed female mice was reduced after week 89 (final survival: 37/50; 19/50; 21/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Nephropathy occurred with increased severity in chemically exposed male rats. The incidences of parathyroid hyperplasia, fibrous osteodystrophy, mineralization of the pulmonary artery, renal cortical cysts, and hyperplasia of the pelvic epithelium were increased in chemically exposed male rats. The incidence of nephropathy was increased in chemically exposed female rats (vehicle control, 29/50; low dose, 48/50; high dose, 39/50). Renal atypical tubular cell hyperplasia and renal tubular cell adenocarcinomas occurred in chemically exposed female rats (atypical tubular cell hyperplasia: 0/50; 1/50; 3/50; tubular cell adenocarcinomas: 0/50; 1/50; 4/50). No renal tubular cell adenocarcinomas have been observed in 2,094 female corn oil vehicle control F344/N rats in National Toxicology Program studies.

Chronic inflammation, ulcers, and epithelial hyperplasia of the forestomach were observed at increased incidences in chemically exposed male rats (chronic inflammation: 1/50; 11/50; 6/49; ulcers: 1/50; 5/50; 8/49; epithelial hyperplasia: 9/50; 15/50; 18/49).

Metaplastic hepatocytes arising within pancreatic islets occurred at an increased incidence in high dose female rats (0/50; 1/50; 11/49).

The incidences of neurilemomas were markedly increased above the historical control incidences (0.1%-0.4%) in all groups of rats (male: 18/50; 13/50; 14/50; female: 7/50; 9/50; 3/50).

Syncytial alteration of the liver occurred at increased incidences in male mice exposed to benzofuran. The incidences of hepatocellular adenomas, hepatoblastomas (high dose male mice) and hepatocellular adenomas, hepatocellular carcinomas, or hepatoblastomas (combined) were increased in chemically exposed mice (male--adenomas: 4/49; 24/39; 34/48; hepatoblastomas: 0/49; 3/39; 18/48; carcinomas, adenomas, or hepatoblastomas, combined: 12/49; 31/39; 40/48; female--adenomas: 1/50; 22/48; 21/47; hepatoblastomas: 0/50; 1/48; 2/47; carcinomas, adenomas, or hepatoblastomas, combined: 4/50; 25/48; 22/47).

Squamous cell papillomas or carcinomas (combined) of the forestomach were increased in chemically exposed mice (male: 2/49; 11/39; 13/48; female: 2/50; 9/50; 5/50).

The incidences of epithelial hyperplasia of the bronchioles were increased in chemically exposed mice. The incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in high dose males and chemically exposed females were increased (adenomas or carcinomas, combined--male: 10/49; 9/39; 19/48; female: 2/50; 9/48; 14/47).

Genetic Toxicology: Benzofuran was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of exogenous metabolic activation. Benzofuran induced trifluorothymidine resistance in mouse L5178Y lymphoma cells treated in the absence of metabolic activation; this assay was not conducted with activation. Benzofuran induced sister chromatid exchanges but not chromosomal aberrations in CHO cells in the presence and absence of activation.

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of benzofuran for male F344/N rats receiving doses of 30 or 60 mg/kg per day. There was *some evidence of carcinogenic activity* of benzofuran for female F344/N rats, based on increased incidences of tubular cell adenocarcinomas of the kidney. There was *clear evidence of carcinogenic activity* for male and female B6C3F$_1$ mice, based on increased incidences of neoplasms of the liver, lung, and forestomach.

Exposure to benzofuran increased the severity of nephropathy in male rats, increased the incidences of nephropathy in female rats, and induced hepatocellular metaplasia in the pancreas in female rats. Nonneoplastic lesions observed in mice exposed to benzofuran included syncytial alteration of the liver, bronchiolar epithelial hyperplasia, and epithelial hyperplasia of the forestomach.

SUMMARY OF THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 30, or 60 mg/kg benzofuran in corn oil, 5 d/wk	0, 60, or 120 mg/kg benzofuran in corn oil, 5 d/wk	0, 60, or 120 mg/kg benzofuran in corn oil, 5 d/wk	0, 120, or 240 mg/kg benzofuran in corn oil, 5 d/wk
Body weights in the 2-year study			
High dose lower than vehicle controls	High dose lower than vehicle controls	Dosed lower than vehicle controls	Dosed lower than vehicle controls
Survival rates in the 2-year study			
33/50; 12/50; 18/50	27/50; 23/50; 25/50	33/50; 20/50; 28/50	37/50; 19/50; 21/50
Nonneoplastic effects			
Increased severity of nephropathy	Kidney: nephropathy; atypical tubular cell hyperplasia (0/50; 1/50; 3/50); pancreatic islets: metaplastic hepatocytes (0/50; 1/50; 11/49)	Liver: syncytial alteration (4/49; 18/39; 36/48); lung: bronchiolar epithelial hyperplasia (3/49; 11/39; 14/48); forestomach: epithelial hyperplasia (16/49; 13/39; 24/48)	Liver: syncytial alteration (1/50; 0/48; 2/47); lung: bronchiolar epithelial hyperplasia (1/50; 22/48; 34/47); forestomach: epithelial hyperplasia (7/50; 19/48; 13/47)
Neoplastic effects			
None	Kidney: tubular cell adenocarcinomas (0/50; 1/50; 4/50)	Liver: hepatocellular adenomas (4/49; 24/39; 34/48); hepatoblastomas (0/49; 3/39; 18/48); hepatocellular adenomas, hepatocellular carcinomas, or hepatoblastomas (combined) (12/49; 31/39; 40/48); forestomach: squamous cell papillomas or carcinomas (combined) (2/49; 11/39; 13/48); lung: alveolar/bronchiolar adenomas or carcinomas (combined) (10/49; 9/39; 19/48)	Liver: hepatocellular adenomas (1/50; 22/48; 21/47); lung: alveolar/bronchiolar adenomas or carcinomas (combined) (2/50; 9/48; 14/47); forestomach: squamous cell papillomas or carcinomas (combined) (2/50; 9/50; 5/50)
Level of evidence of carcinogenic activity			
No evidence	Some evidence	Clear evidence	Clear evidence

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Benzofuran is based on 13-week studies that began in January 1980 and ended in April 1980 and on 2-year studies that began in January 1981 and ended in February 1983 at Springborn Institute for Bioresearch, Inc. (Spencerville, OH).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on benzofuran on March 13, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZOFURAN

On March 13, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of benzofuran received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R. Irwin, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male rats, some evidence of carcinogenic activity for female rats, clear evidence of carcinogenic activity for male and female mice).

Dr. Irwin reported an unusually high incidence of neurilemomas in the vehicle control and chemically exposed rats of each sex. Dr. M.P. Jokinen, NIEHS, described the origins, anatomic characteristics, and patterns of occurrence of these neoplasms of peripheral nerve sheaths. Dr. Irwin said that there was no apparent explanation for the high incidence of these uncommon neoplasms.

Dr. Newberne, a principal reviewer, agreed with the conclusions. He suggested that the poor survival of male rats might have obscured possible neoplastic effects in the kidney. He noted that there were two separate lots of chemical used and inquired as to how they were phased into the studies. Dr. Irwin said that one lot was used for the 14-day and 13-week studies and the second lot was used for all animals in the 2-year studies. Dr. J. Huff, NIEHS, indicated that the two lots were of equal purity.

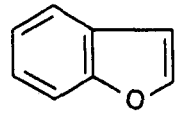
Dr. McKnight, the second principal reviewer, agreed with the conclusions; she added that she could support changing the conclusion for female rats to clear evidence of carcinogenic activity because renal tubular cell adenomas are so rare in female rats and because the study showed a clear dose-related trend. Dr. Irwin said that there was no unanimity among the staff on the level of evidence but the consensus was that the incidence was not significant enough for clear evidence. Dr. McKnight asked about the 10 male mice that died early in the study as a result of an overdose and wondered if these should have been included in the statistical analyses. Dr. Irwin commented that since the mice died during week 20 or 21, they were really not yet at risk and so it was considered appropriate to censor them.

Dr. Gold, the third principal reviewer, agreed with the conclusions. She asked for additional information on the relationship between renal hyperplasia and neoplasia in these rat studies and, specifically, about the incidence of hyperplasia and the severity of nephropathy in the individual female rats with tubular cell adenocarcinomas compared with the incidence of hyperplasia and severity of nephropathy in female rats without kidney tumors. Dr. Irwin said that none of the rats that had kidney tumors had tubular cell hyperplasia. Dr. Huff mentioned that for certain tumors, all stages of the biologic continuum might not be found and, in some cases, malignant neoplasia may arise in situ.

Dr. Newberne moved that the Technical Report on benzofuran be accepted with the revisions discussed and the conclusions as written for male rats, no evidence of carcinogenic activity, for female rats, some evidence of carcinogenic activity, and for male and female mice, clear evidence of carcinogenic activity. Dr. Gold seconded the motion, which was accepted unanimously by the Panel.

I. INTRODUCTION

I. INTRODUCTION



BENZOFURAN

CAS No. 271-89-6

C_8H_6O Molecular weight 118.1

Synonyms: Coumarone; cumarone

Benzofuran is a clear, faintly yellow liquid with an aromatic odor. It is insoluble in water but miscible with benzene, petroleum ether, and other organic solvents. At atmospheric pressure (760 mm mercury), benzofuran boils at 173°-175° C and freezes at −28° C. Benzofuran is a minor component of coal tar distillate and is prepared as a by-product of the crude heavy solvent fraction, which also includes light oils and resin formers such as indene and dicyclopentadiene (Kirk-Othmer, 1980).

The major industrial use of benzofuran is in the production of coumarone (benzofuran)-indene hydrocarbon resins (Kirk-Othmer, 1980). The resins are polymerized by the addition of a boron trifluoride catalyst to a specific coal tar distillate fraction that contains approximately 30% indene and a small amount of benzofuran. The resins have been used in rubber compounding, as liquid plasticizers, in coatings such as aluminum paints and varnishes, in corrosion-resistant coatings, and in water-resistant coatings for paper products and fabrics. In addition, coumarone-indene resins have been approved for use in adhesives for food containers. Current production information is not available for benzofuran or for coumarone-indene resins.

The benzofuran structure is present in a series of β blockers and antiarrhythmic drugs including amiodarone (2-butyl-3-(3,5,-diiodo-4-(β-diethylaminoethoxy)-benzoyl)benzofuran), bufuralol (7-ethyl-α-((*t*-butylamino)-methyl)2-benzofuran), and the uricosuric agent benzbromarone (2-ethyl-3(4-hydroxy-3,5-dibromobenzoyl)benzofuran).

Benzofuran is a member of a group of compounds containing an unsaturated furan ring. Although only one published report deals specifically with the toxicity of benzofuran, studies of several other furan compounds indicate that the toxicity associated with this group of compounds invariably involves cell death and necrosis in the target tissue, most often the liver, kidney, or lung (Boyd, 1980, 1981; Burka and Boyd, 1985). For those compounds that have been examined in detail, cell death correlates with cytochrome P450 bioactivation of the furan ring to a reactive intermediate that covalently attaches to cellular components. Although a furan epoxide has been proposed as a possible candidate for the reactive intermediate, recent studies indicate that for simple alkyl substituted furans, bioactivation leads to cleavage of the furan ring with formation of the corresponding dialdehyde (Ravindranath et al., 1984).

In short-term studies, oral administration of furan compounds most often caused hepatic and/or renal necrosis in rats and mice. Mice given 100 mg/kg benzofuran by intraperitoneal injection developed renal necrosis 36 hours after compound administration, whereas administration of 200 mg/kg benzofuran caused both renal and hepatic necrosis (McMurtry and Mitchell, 1977). The target organ most severely affected depends on the specific furan compound administered, and treatments that selectively induce or inhibit cytochrome P450 activity alter the severity of necrosis. For example, pretreatment of mice with phenobarbital or piperonyl butoxide decreased the renal necrosis observed after intraperitoneal injection of benzofuran, whereas pretreatment with cobaltous chloride reduced both the renal and hepatic necrosis.

The carcinogenic potential of benzofuran was evaluated in a 12-month study in which albino rats (strain not specified) were exposed (dose not specified) by subcutaneous implantation (Stankevich, 1962). At the end of the study, an 8.5% incidence of subcutaneous fibromas was found in

chemically exposed animals; no data were presented for control animals. This study was considered inadequate for evaluation of carcinogenic potential because of the short study duration and the lack of adequate data on controls or chemical dosage.

The mutagenicity of benzofuran in *Salmonella typhimurium* has been examined in several studies. Benzofuran of 97% or greater purity was negative in qualitative spot tests in strains TA98, TA100, TA1535, or TA1537 in the presence or absence of liver S9 from Aroclor 1254-induced rats and in a quantitative plate incorporation assay (0.03-30 µmol/plate) using TA98 in the presence or absence of liver S9 from three methylcholanthrene-induced rats (Florin et al., 1980). In another study, using the standard plate incorporation assay and chemical concentrations ranging from toxic concentrations down to 10^{-4} of the toxic concentration (purity and actual concentrations of benzofuran not stated), no increase in revertants per plate was found in strains TA98, TA98NR, TA100, TA1535, TA1537, or TA1538 in the presence or absence of liver S9 from Aroclor 1254-induced rats (Weill-Thevenet et al., 1981). Negative results were also obtained with preincubation assays in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 at benzofuran concentrations up to 1,000 µg per plate (Haworth et al., 1983) and in strains TA98 and TA100 from toxic concentrations down to 10^{-4} of the toxic concentration.

Benzofuran was nominated for toxicology and carcinogenesis studies by the National Cancer Institute because of potential human exposure associated with its use in coumarone-indene resins and its detection in the surface waters surrounding major industrial areas (NCI, 1978).

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF BENZOFURAN

CHARACTERIZATION OF DOSE MIXTURES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF BENZOFURAN

Benzofuran was obtained as a clear yellow liquid in two lots from Riches-Nelson, Inc. (Greenwich, CT). Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G).

Both lots of the study chemical were identified as benzofuran by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Both lots were found to be approximately 99% pure, as determined by elemental analysis, Karl Fischer water analysis, and gas chromatography.

Stability of the bulk chemical during the toxicology studies was monitored by gas chromatography and ultraviolet spectroscopy. No deterioration of the study material was seen over the course of the studies.

CHARACTERIZATION OF DOSE MIXTURES

The stability of benzofuran in corn oil at 20 mg/ml was investigated by storing samples in the dark at room temperature or at 5° C for 7 or 14 days. The concentration of benzofuran in samples stored at room temperature decreased 2.7% and 5.5% after 7 and 14 days, respectively. The same solution stored at 5° C had losses of 2.5% and 4.4% after 7 and 14 days' storage. Based on the results of the stability study, the dose mixtures were stored at about 4° C for no longer than 7 days throughout the studies.

During the 2-year studies, the dose mixtures were analyzed at approximately 8-week intervals. For the benzofuran studies, it was estimated that the mixtures were formulated within ±10% of the target concentrations approximately 98% (44/45) of the time throughout the studies (Table G4). The one dose mixture out of specification was prepared on June 19, 1981, for low dose male mice and was found to have a concentration of 24 mg/ml instead of the required 6 mg/ml. Results of periodic referee analysis performed by the analytical chemistry laboratory indicated excellent agreement with the results from the study laboratory (Table G5).

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and were held for 17 days before the studies began. The rats were 5-8 weeks old when placed on study, and the mice were 7-9 weeks old.

Groups of five rats of each sex were administered 62.5, 125, 250, 500, or 1,000 mg/kg benzofuran in corn oil by gavage for 14 consecutive days. Groups of five mice of each sex were administered 15.63, 31.25, 62.5, 125, or 250 mg/kg benzofuran on the same schedule. Controls were untreated.

Animals were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed two times per day and were weighed on days 0, 7, and 15. A necropsy was performed on all animals. Histologic examinations were performed on three males and three females in the 250 mg/kg groups of rats and mice. Further details are presented in Table 1.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of benzofuran and to determine the doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 18 days, and assigned to cages according to a table of random numbers. Cages were assigned to groups according to another table of random numbers. Rats were 7-8 weeks old when placed on study, and mice were 7 weeks old.

Groups of 10 rats and mice of each sex were administered 0, 31.25, 62.5, 125, 250, or 500 mg/kg benzofuran in corn oil by gavage, 5 days per week for 13 weeks.

Rats and mice were housed five per cage. Feed and water were available ad libitum. Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded once per week. Further experimental details are summarized in Table 1.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BENZOFURAN

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
Rats--62.5, 125, 250, 500, or 1,000 mg/kg benzofuran in corn oil by gavage; mice--15.63, 31.25, 62.5, 125, or 250 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg; controls were untreated	0, 31.25, 62.5, 125, 250, or 500 mg/kg benzofuran in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--male: 0, 30, or 60 mg/kg benzofuran in corn oil by gavage; female: 0, 60, or 120 mg/kg; mice--male: 0, 60, or 120 mg/kg; female: 0, 120, or 240 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg
Date of First Dose		
10/28/79	1/14/80	Rats--1/29/81; mice--2/5/81
Date of Last Dose		
11/11/79	4/11/80	Rats--1/19/83; mice--1/26/83
Duration of Dosing		
1 × d for 14 consecutive d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter	Same as 14-d studies	Observed 2 × d; weighed 1 × wk for 12 wk and then at least 1 × mo
Necropsy and Histologic Examinations		
Necropsy performed on all animals; histologic exams performed on 3 males and 3 females in the 250 mg/kg groups; tissues examined include adrenal glands, bone marrow, brain, colon, costochondral junction, duodenum, esophagus, external and middle ear, eyes, heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, pancreas, parathyroids, pituitary gland, rectum, regional lymph nodes, salivary glands, sciatic nerve, seminal vesicles/prostate/testes or ovaries/uterus, skin, spinal cord, spleen, stomach, thigh muscle, thymus, thyroid gland, trachea, and urinary bladder	Necropsy performed on all animals; histologic exams performed on all vehicle control and high dose animals and all animals dying before the end of the studies; tissues examined are the same as for the 14-d studies. Adrenal glands (250 mg/kg group only), kidneys, and liver examined for the 125 and 250 mg/kg groups of rats and kidneys examined for the 125 and 250 mg/kg groups of mice	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups and low dose male rats: adrenal glands, brain, esophagus, eyes (if grossly abnormal), gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, kidneys, large intestine, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroids, pharynx (if grossly abnormal), pituitary gland, prostate/testes/epididymis or ovaries/uterus, salivary glands, skin, small intestine, spinal cord (if neurologic signs present), spleen, sternebrae or vertebrae or femur including marrow, stomach, thymus, thyroid gland, trachea, and urinary bladder. Tissues examined for low dose female rats include gross lesions, heart, kidneys, liver, lungs, pancreas, pituitary gland, spleen, thyroid gland, and uterus. Tissues examined for low dose mice: adrenal glands (males), gross lesions, kidney, liver, lungs, nasal cavity, pituitary gland (females), stomach, and uterus
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BENZOFURAN (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Study Laboratory Springborn Institute for Bioresearch, Inc.	Springborn Institute for Bioresearch, Inc.	Springborn Institute for Bioresearch, Inc.
Time Held Before Study 17 d	18 d	14 d
Age When Placed on Study Rats--5-8 wk; mice--7-9 wk	Rats--7-8 wk; mice--7 wk	Rats--6-7 wk; mice--7-8 wk
Age When Killed Rats--7-10 wk; mice--9-11 wk	Rats--20-21 wk; mice--20 wk	Rats--110-111 wk; mice--111-112 wk
Necropsy or Kill Dates 11/12/79	4/14/80-4/15/80	Rats--1/26/83-1/28/83; mice--2/2/83-2/4/83
Method of Animal Distribution Assigned to cages according to a table of random numbers	Assigned to cages by one table of random numbers and then to groups according to another table of random numbers	Same as 13-wk studies
Diet NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 14-d studies	Same as 14-d studies
Bedding Anipads (Ancare Corp.)	Ancubes (Ancare Corp.)	Heat-treated hardwood chips (Ancare Corp., Manhassett, NY)
Water Tap water in glass bottles; available ad libitum	Automatic watering system; half deionized, half tap water available ad libitum	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum; approximately 90% of the dissolved salts removed by a reverse osmosis unit
Cages Stainless steel hanging cages with wire mesh bottoms (Shoreline)	Polycarbonate hanging cages (Lab Products, Inc.)	Same as 13-wk studies
Cage Filters None	100% polyester (Snow Filtration, Cincinnati, OH)	Same as 13-wk studies
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--70°-75° F; hum--41%-71%; fluorescent light 12 h/d; 12 room air changes/h	Temp--70°-77° F; hum--36%-74%; fluorescent light 12 h/d; 12 room air changes/h	Temp--73.1° ± 2.0° F (range, 64°-81° F); hum--57.2% ± 14.2% (range, 18%-96%); fluorescent light 12 h/d; 12 room air changes/h

At the end of the 13-week studies, survivors were killed and a necropsy was performed on all animals. Histologic examinations were performed on all vehicle control animals, all animals that died before the scheduled kill, and all animals in the 500 mg/kg groups. Tissues and groups examined are listed in Table 1.

TWO-YEAR STUDIES

Study Design

Groups of 50 male rats were administered 0, 30, or 60 mg/kg benzofuran in corn oil by gavage, 5 days per week for 103 weeks, and groups of 50 female rats were administered 0, 60, or 120 mg/kg. Groups of 50 male mice were administered 0, 60, or 120 mg/kg on the same schedule, and groups of 50 female mice were administered 0, 120, or 240 mg/kg.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 4-5 weeks (rats) or 5-6 weeks (mice) of age. The animals were quarantined at the study laboratory for 2 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 6-7 weeks of age and the mice at 7-8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

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

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed (Appendix F) and water were available ad libitum. Cages were rotated during these studies. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed twice per day. Body weights were recorded once per week for the first 12 weeks of the studies and at least once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals.

During necropsy, all organs were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to the "inverse pyramid" design (McConnell, 1983a,b). Complete histopathologic examinations (Table 1) were performed on vehicle control animals, male rats in the 60 mg/kg group, female

rats and male mice in the 120 mg/kg groups, and female mice in the 240 mg/kg group and on all animals dying early in the studies, including those in lower dose groups. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose groups were examined histopathologically.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Carcinogenesis Bioassay Data System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues, and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Target organs were the kidney, pancreas, and thyroid gland for male and female rats; spleen and stomach for male rats; lung for female rats; and liver, forestomach, lung, and nose for male and female mice. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs, the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends. Tissues are generally not evaluated in a "blinded" fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle.

The quality assessment report and slides were submitted to a Pathology Working Group (PWG) Chairperson, who reviewed microscopically all potential target tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related nonneoplastic lesions and neoplasms and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were shown to the PWG. The PWG, which included the laboratory pathologist, the quality assessment pathologist, and other pathologists experienced in rodent toxicology, examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final pathology data represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Statistical Methods

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g.,

skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was an incidental tumor analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined to obtain a single overall result.

In addition to incidental tumor analysis, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart et al., 1979), procedures based on the overall proportion of tumor-bearing animals.

Tests of significance include pairwise comparisons of each dosed group with vehicle controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

GENETIC TOXICOLOGY

III. RESULTS: RATS

FOURTEEN-DAY STUDIES

All male and female rats that received 1,000 mg/kg and one female that received 500 mg/kg died before the end of the studies (Table 2). The final mean body weights of male rats that received 250 or 500 mg/kg were 13% or 21% lower than that of controls; the final mean body weight of females that received 500 mg/kg was 10% lower than that of controls. Decreased motor activity, pallor, and a red ocular and nasal discharge were observed in animals that received 500 or 1,000 mg/kg. No compound-related histopathologic lesions were found.

THIRTEEN-WEEK STUDIES

One female rat that received 500 mg/kg and one female that received 250 mg/kg died before the end of the studies (Table 3). The final mean body weights of male rats that received 125, 250, or 500 mg/kg were 11%, 17%, or 27% lower than that of vehicle controls; the final mean body weight of females that received 500 mg/kg was 11% lower than that of vehicle controls. Salivation after dosing was observed in all chemically exposed rats. Reduced motor activity was observed for both males and females that received 125, 250, or 500 mg/kg, and excessive urination was observed for females that received 62.5, 125, 250, or 500 mg/kg.

Compound-related lesions were present in the liver, kidney, and adrenal glands. Necrosis of hepatocytes occurred in the liver of male and female rats that received 250 or 500 mg/kg benzofuran and in males that received 125 mg/kg. The lesions consisted of minimal centrilobular degeneration and necrosis of individual hepatocytes throughout the liver parenchyma; some increased mitotic activity was also evident.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF BENZOFURAN

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	5/5	149 ± 4	227 ± 6	+ 78 ± 4	
62.5	5/5	146 ± 4	210 ± 4	+ 64 ± 2	93
125	5/5	147 ± 4	211 ± 3	+ 64 ± 3	93
250	5/5	138 ± 5	198 ± 8	+ 60 ± 3	87
500	5/5	149 ± 4	179 ± 5	+ 30 ± 4	79
1,000	(e) 0/5	144 ± 7	(f)	(f)	(f)
FEMALE					
(d) 0	5/5	111 ± 2	137 ± 2	+ 26 ± 2	
62.5	5/5	112 ± 3	141 ± 4	+ 29 ± 2	103
125	5/5	110 ± 2	141 ± 2	+ 31 ± 2	103
250	5/5	109 ± 1	136 ± 2	+ 27 ± 1	99
500	(g) 4/5	111 ± 2	123 ± 5	+ 11 ± 4	90
1,000	(h) 0/5	108 ± 1	(f)	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Controls were untreated.
(e) Day of death: 2,3,3,3,3
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: 4
(h) Day of death: all 3

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BENZOFURAN

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	139 ± 3	349 ± 5	+ 210 ± 4	
31.25	10/10	142 ± 2	343 ± 6	+ 201 ± 6	98
62.5	10/10	138 ± 2	339 ± 6	+ 201 ± 6	97
125	10/10	145 ± 2	309 ± 7	+ 164 ± 7	89
250	10/10	143 ± 3	291 ± 4	+ 148 ± 3	83
500	10/10	146 ± 3	256 ± 7	+ 110 ± 5	73
FEMALE					
0	10/10	115 ± 1	195 ± 2	+ 80 ± 2	
31.25	10/10	112 ± 1	198 ± 2	+ 86 ± 2	102
62.5	10/10	117 ± 2	193 ± 4	+ 76 ± 2	99
125	10/10	110 ± 1	181 ± 1	+ 71 ± 1	93
250	(d) 9/10	111 ± 2	188 ± 2	+ 76 ± 1	96
500	(e) 9/10	110 ± 2	174 ± 4	+ 64 ± 3	89

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 1
(e) Week of death: 5

Nephropathy occurred with increased severity in male rats that received 250 or 500 mg/kg. Histologically, the nephropathy was characterized by foci of tubular regeneration and dilated tubules containing hyaline casts. These changes are consistent with spontaneous nephropathy that was exacerbated in male rats in the 250 and 500 mg/kg groups. Nephropathy similar to that present in males occurred with minimal-to-mild severity in female rats that received 250 or 500 mg/kg but was not observed in vehicle controls or in lower dose groups of female rats.

Cytoplasmic vacuolization of the adrenal cortex occurred in all male and female rats that received 500 mg/kg, in 2/10 males that received 250 mg/kg, and in 1/10 vehicle control males.

Dose Selection Rationale: Because of the increased severity of nephropathy that occurred at the two highest doses in males and at the high dose in females, the presence of hepatocellular necrosis at doses of 125 mg/kg or higher in males, and reduced body weights, doses selected for rats for the 2-year studies were 30 and 60 mg/kg benzofuran in corn oil for males and 60 and 120 mg/kg benzofuran for females, administered by gavage 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were generally 6%-11% lower than those of vehicle controls after week 24 (Table 4 and Figure 1). Mean body weights of low dose male rats were 5%-9% lower than those of vehicle controls after week 77. Mean body weights of high dose female rats were generally 4%-8% lower than those of vehicle controls after week 20. Mean body weights of low dose female rats were similar to those of vehicle controls throughout the study.

TABLE 4. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of veh. controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of veh. controls)	High Dose No. of Survivors
MALE				**30 mg/kg**			**60 mg/kg**	
1	163	50	168	103	50	163	100	50
2	196	50	201	103	50	197	101	50
3	213	50	221	104	50	210	99	50
4	235	50	236	100	50	227	97	50
5	236	50	251	106	50	231	98	50
6	255	50	266	104	50	253	99	50
7	266	50	279	105	50	263	99	50
8	272	50	294	108	50	270	99	50
9	295	50	311	105	50	285	97	50
10	309	50	316	102	50	298	96	50
11	316	50	327	103	50	307	97	50
12	328	50	335	102	50	317	97	50
16	355	50	357	101	50	332	94	50
20	364	50	371	102	50	347	95	50
24	394	50	394	100	50	369	94	50
28	423	50	415	98	50	391	92	50
32	433	50	428	99	50	407	94	50
36	452	50	444	98	50	419	93	50
40	452	50	430	95	50	410	91	50
44	449	50	446	99	50	418	93	50
48	451	50	432	96	49	413	92	50
52	456	50	442	97	49	411	90	50
56	460	50	442	96	49	413	90	49
60	446	50	447	100	49	415	93	48
64	464	50	461	99	49	430	93	48
68	476	50	467	98	49	440	92	48
72	474	50	459	97	49	459	97	47
77	472	49	444	94	48	436	92	42
81	452	49	429	95	47	417	92	42
85	464	48	434	94	45	424	91	40
89	459	47	422	92	39	415	90	38
95	454	41	417	92	24	409	90	27
99	452	36	421	93	18	416	92	22
101	457	34	416	91	16	405	89	21
FEMALE				**60 mg/kg**			**120 mg/kg**	
1	117	50	118	101	50	116	99	49
2	133	50	139	105	50	139	105	48
3	141	50	141	100	50	141	100	47
4	151	50	149	99	50	146	97	47
5	156	50	163	104	50	156	100	47
6	160	50	167	104	50	159	99	47
7	168	50	170	101	50	166	99	47
8	172	50	174	101	50	177	103	47
9	179	50	180	101	50	178	99	47
10	183	50	186	102	50	181	99	46
11	186	50	191	103	50	186	100	46
12	193	50	193	100	50	190	98	46
16	203	50	202	100	50	198	98	46
20	209	50	211	101	50	200	96	46
24	221	50	223	101	50	213	96	46
28	230	50	231	100	50	221	96	46
32	235	50	238	101	50	228	97	46
36	242	50	247	102	50	232	96	46
40	245	50	247	101	50	232	95	45
44	252	50	256	102	50	239	95	45
48	252	49	259	103	50	232	92	45
52	258	49	264	102	50	241	93	45
56	267	49	275	103	50	256	96	45
60	275	49	285	104	49	264	96	44
64	286	49	290	101	49	269	94	44
68	305	48	313	103	48	290	95	43
72	311	48	315	101	48	294	95	43
77	318	47	315	99	45	300	94	41
81	315	47	312	99	43	289	92	41
85	317	45	313	99	43	297	94	38
89	309	43	326	106	41	307	99	34
95	325	35	325	100	33	306	94	29
99	324	33	326	101	30	310	96	28
101	330	29	329	100	26	313	95	26

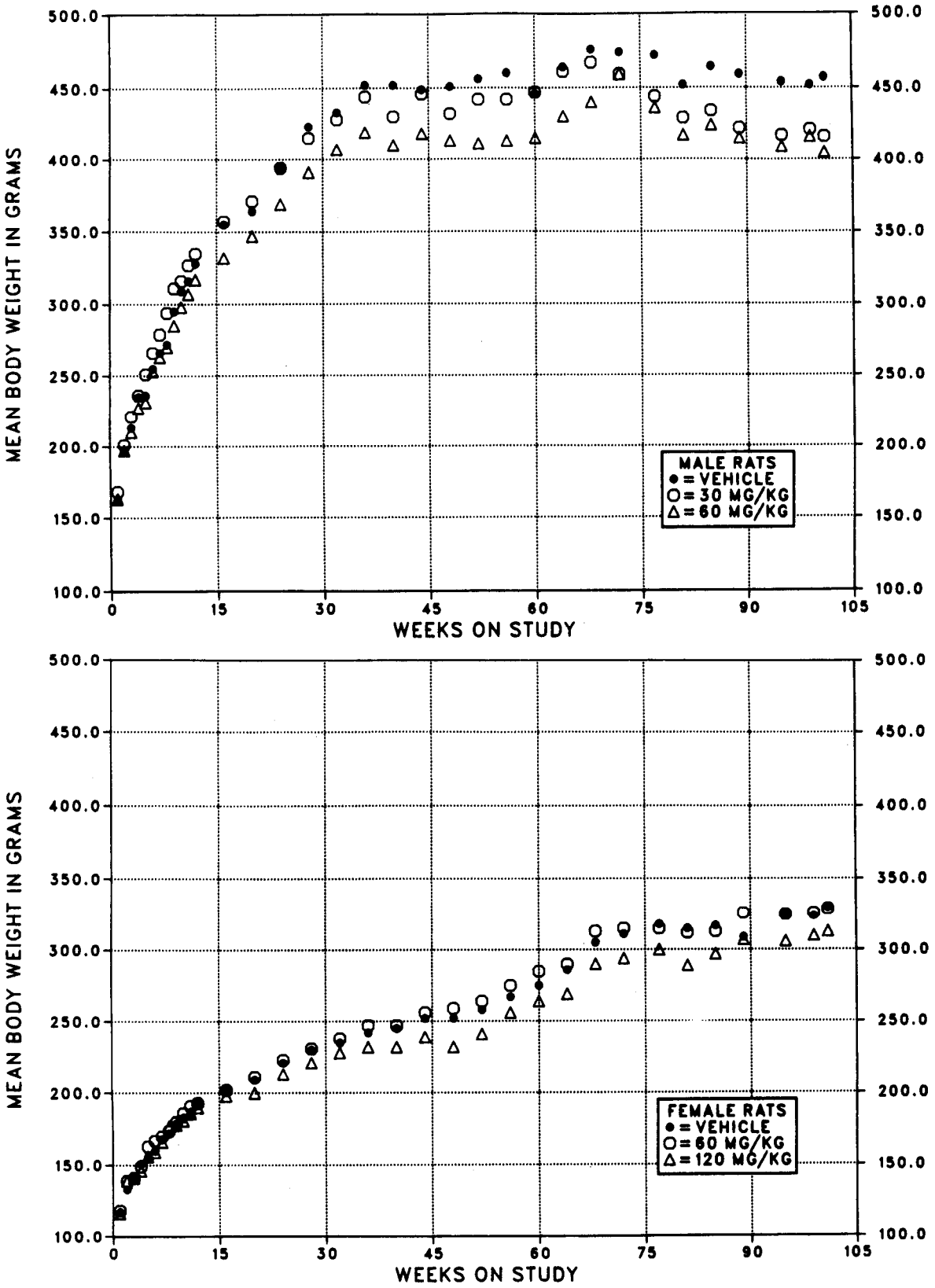


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED BENZOFURAN IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: RATS

Survival

Estimates of the probabilities of survival for male and female rats administered benzofuran at the doses used in these studies and for vehicle controls are shown in Table 5 and in the Kaplan and Meier curves in Figure 2. The survival of both the low (after week 90) and the high (after week 92) dose groups of male rats was significantly lower than that of the vehicle controls. No significant differences in survival were observed between any groups of female rats.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the kidney, parathyroids, pulmonary artery, peripheral nerves, hematopoietic system, lung, thyroid gland, tongue and palate, pituitary gland, pancreatic islets, forestomach, and mammary gland.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

Kidney: Nephropathy occurred in nearly all male rats, but the severity of this age-related disease was increased in chemically exposed male rats; the incidence and severity of nephropathy were also increased in dosed female rats (Table 6). The nephropathy was characterized by tubular degeneration and atrophy, dilated tubules containing hyaline and granular casts, tubular regeneration, glomerulosclerosis, interstitial fibrosis, and chronic inflammation. Cortical cysts and papillary hyperplasia of the pelvic epithelium, changes associated with advanced nephropathy, were also increased in chemically exposed male rats. Marked nephropathy is considered to be responsible for the reduced survival of chemically exposed males after week 90.

TABLE 5. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
MALE (a)				
Animals initially in study	50	50	50	
Natural deaths	2	13	11	
Moribund kills	15	25	20	
Animals surviving until study termination	33	12	18	
Killed accidentally	0	0	1	
Survival P values (b)	0.003	<0.001	0.003	
FEMALE (a)				
Animals initially in study	50		50	50
Natural deaths	6		5	7
Moribund kills	17		22	14
Animals surviving until study termination	27		23	25
Killed accidentally	0		0	4
Survival P values (b)	0.802		0.514	0.888

(a) Termination period: week 104
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

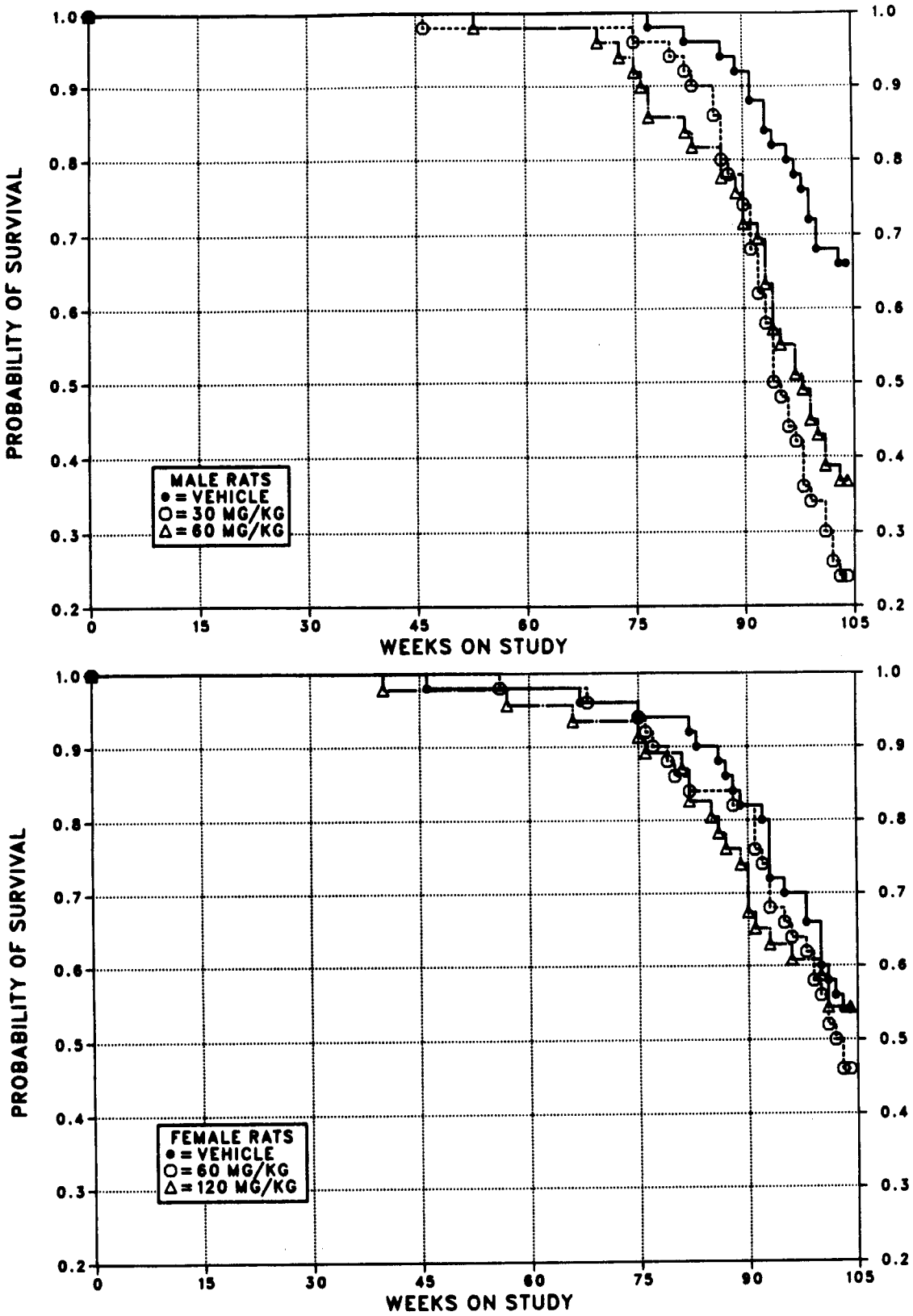


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED BENZOFURAN IN CORN OIL BY GAVAGE FOR TWO YEARS

TABLE 6. INCIDENCES OF RATS WITH RENAL LESIONS AND LESIONS CONSIDERED SECONDARY TO NEPHROPATHY IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN

Lesion	Male			Female		
	Vehicle Control	30 mg/kg	60 mg/kg	Vehicle Control	60 mg/kg	120 mg/kg
Nephropathy	49/50	49/50	48/49	29/50	**48/50	*39/50
Severity (a)						
Minimal	24	3	3	24	21	22
Mild	19	7	11	5	18	14
Moderate	5	10	20	0	7	3
Marked	1	29	14	0	2	0
Renal cortical cyst	0/50	**16/50	*6/49	0/50	1/50	1/50
Renal pelvis papillary hyperplasia	1/50	**22/50	**8/49	0/50	1/50	0/50
Renal atypical tubular cell hyperplasia	0/50	0/50	1/49	0/50	1/50	3/50
Parathyroid hyperplasia	0/40	**8/38	3/36	0/33	0/7	1/38
Fibrous osteodystrophy	0/50	4/50	3/50	0/50	0/50	0/50
Mineralization of pulmonary artery	10/50	**23/50	3/50	4/50	*13/50	0/50
Renal focal infarct	0/50	0/50	1/49	1/50	0/50	6/50
Tubular cell adenoma	1/50	1/50	0/49	0/50	0/50	0/50
Tubular cell adenocarcinoma	0/50	0/50	0/49	0/50	1/50	*4/50

(a) Number of rats with indicated severity
*P<0.05 vs. the vehicle controls
**P<0.01 vs. the vehicle controls

Atypical tubular cell hyperplasia and tubular cell adenocarcinomas were increased in chemically exposed female rats (Tables 6 and 7). Atypical tubular cell hyperplasia consisted of small, well-demarcated collections of tubular cells in the cortex of affected kidneys (Figure 3). Cells forming the lesions were round to polygonal with abundant eosinophilic, finely granular cytoplasm and had eccentric nuclei with prominent nucleoli. Proliferative lesions consisting of similar cells have been described previously in rats and were designated as oncocytomas (Bannasch et al., 1986). During the review of the lesions that occurred in the current studies, however, the NTP Pathology Working Group considered these to be hyperplastic rather than neoplastic lesions.

The atypical tubular cell hyperplasia was not part of a morphologic continuum with the tubular cell adenocarcinomas. The adenocarcinomas were nodular masses, 0.1-1.5 cm in diameter, in the cortex of the kidney (Figure 4). They were composed of closely packed solid nests or tubular-like structures of plump, polygonal cells with eosinophilic cytoplasm and large, oval nuclei; mitotic figures were frequent. Focal necrosis and/or dilated cyst-like spaces were features of some of the neoplasms. Tubular cell neoplasms are uncommon in female F344/N rats; adenomas have occurred in corn oil vehicle controls at a historical incidence of 0.1%, but no adenocarcinomas have been observed.

Parathyroids and Pulmonary Artery: Increased incidences of parathyroid hyperplasia, fibrous osteodystrophy, and mineralization of the pulmonary artery occurred in chemically exposed male rats, particularly in the low dose group. These lesions are believed to represent the effects of renal secondary hyperparathyroidism associated with chronic renal disease. The lack of a strong dose-related effect in the high dose male rats is likely due to the reduced survival in that group.

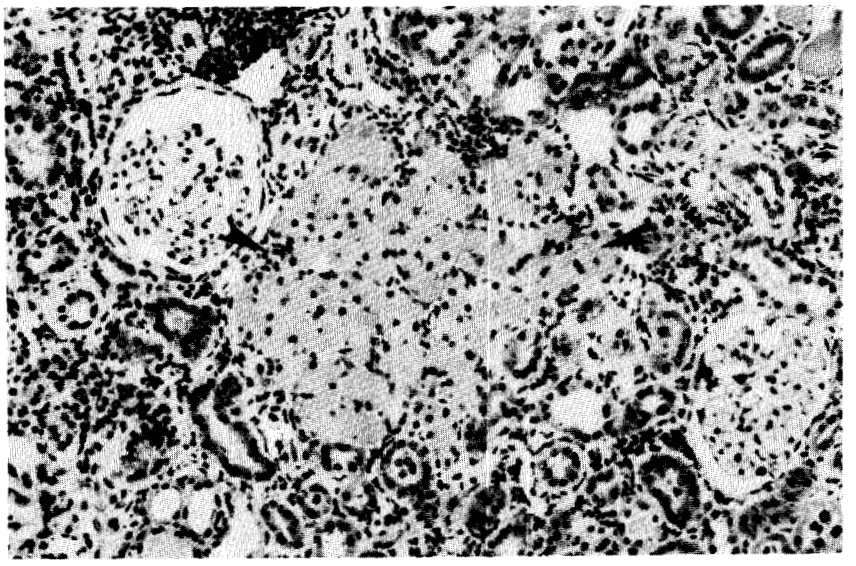


Figure 3. Atypical tubular cell hyperplasia ("oncocytic hyperplasia") in kidney of low dose female rat no. 1 (arrows).

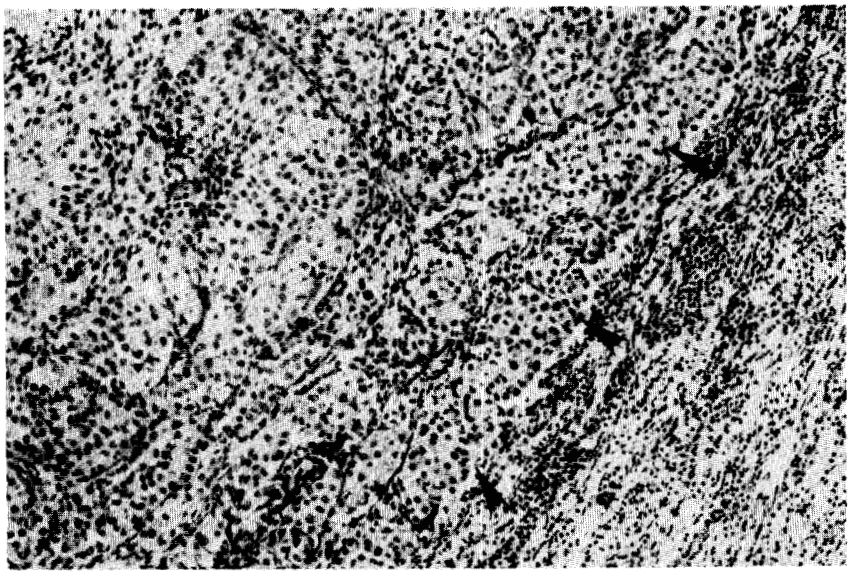


Figure 4. Tubular cell adenocarcinoma in kidney of high dose female rat no. 19. The margin of the neoplasm is denoted by arrows.

TABLE 7. RENAL TUBULAR CELL TUMORS IN FEMALE RATS IN THE TWO-YEARGAVAGE STUDY OF BENZOFURAN (a)

	Vehicle Control	60 mg/kg	120 mg/kg
Adenocarcinoma (b)			
Overall Rates	0/50 (0%)	1/50 (2%)	4/50 (8%)
Terminal Rates	0/27 (0%)	0/23 (0%)	3/25 (12%)
Week of First Observation		103	101
Incidental Tumor Tests	P=0.009	P=0.515	P=0.032

(a) For a complete explanation of the entries in this table, see Table B3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of renal tubular cell adenomas at study laboratory (mean ± SD): 1/149 (0.7% ± 1%); historical incidence in NTP studies: 2/2,094 (0.1% ± 0.4%); no adenocarcinomas have been observed.

Peripheral Nerves: The incidences of malignant neurilemomas were unusually high in all groups of male and female rats (Table 8). Neurilemomas are neoplasms of the peripheral nerve sheath, which may occur at several anatomical locations. In the present studies, the incidences of neurilemomas at all sites have been combined for the purpose of evaluating the effect of chemical exposure.

Hematopoietic System: Mononuclear cell leukemia occurred with a positive trend in male rats by the life table test; the incidences in the chemically exposed groups were greater than that in the vehicle controls (Table 9). The increase was primarily due to the presence of more nonfatal stage-1 leukemia in chemically exposed groups. Moreover, the proportion of animals with leukemia which died before the end of the study was similar in all groups of male rats. It is therefore unlikely that mononuclear cell leukemia contributed to the reduced survival. One additional statistical analysis was carried out for the the staged leukemia data: the procedure of Peto et al. (1980), with the assumption that all stage-3 leukemia observed before the end of the study was "fatal" and all other leukemia was "incidental." The significance of the effect in the high dose group was marginal (P=0.045). After these several analyses, the marginal increase in leukemia was not considered to be chemically related.

Lung: The incidences of alveolar/bronchiolar adenomas were increased in chemically exposed female rats (vehicle control, 0/50; low dose, 1/50; high dose, 3/49), and the incidences of alveolar/bronchiolar carcinomas were marginally increased in male rats (0/50; 3/50; 2/48). The incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in chemically exposed rats were not significantly greater than those in vehicle controls (male: 1/50; 3/50; 2/48; female: 0/50; 2/50; 3/49).

Thyroid Gland: Cystic follicles occurred at increased incidences in chemically exposed male rats and at decreased incidences in chemically exposed females (male: vehicle control, 2/50; low dose, 4/48; high dose, 9/45; female: 4/48; 2/48; 0/49). Although three follicular cell carcinomas occurred in male rats that received 60 mg/kg, the incidences of follicular papillary adenomas or follicular cell carcinomas (combined) in chemically exposed male rats were not significantly greater than that in vehicle controls (2/50; 1/48; 3/45). The low incidence of carcinomas and the lack of an increase in the incidence of adenomas or carcinomas (combined) make it unlikely that these lesions were related to chemical exposure.

TABLE 8. INCIDENCES OF NEURILEMOMAS AT ALL SITES IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN

Tissue	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
MALE (a)				
Subcutaneous tissue	14/50	8/50	6/50	
Heart	3/50	3/49	4/48	
Salivary gland	1/46	2/39	2/41	
Stomach	0/50	0/50	1/49	
Body cavity	0/50	0/50	1/50	
Total	18/50	13/50	14/50	
FEMALE (b)				
Subcutaneous tissue	1/50		9/50	3/50
Heart	3/49		0/50	0/49
Vagina	1/50		0/50	0/50
Ovary	2/50		0/16	0/49
Total	7/50		9/50	3/50

(a) In 36 other NTP studies (including various routes of exposure) started between August 1980 and June 1981, a total of 16 neurilemomas were diagnosed in approximately 1,800 control male F344/N rats; 7 of the 16 were in two studies conducted at the same laboratory as for benzofuran. The range of incidences was 0/50-5/50 (penicillin VK).
(b) In 36 other NTP studies (including various routes of exposure) started between August 1980 and June 1981, a total of 12 neurilemomas were diagnosed in approximately 1,800 control female F344/N rats; 3 of the 12 were in one study conducted at the same laboratory as for benzofuran. The range of incidences was 0/50-3/50 (*N,N*-dimethylaniline).

TABLE 9. HEMATOPOIETIC SYSTEM TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (a)

	Vehicle Control	30 mg/kg	60 mg/kg
Mononuclear Cell Leukemia (b)			
Overall Rates	10/50 (20%)	13/50 (26%)	17/50 (34%)
Terminal Rates	4/33 (12%)	5/12 (42%)	5/18 (28%)
Week of First Observation	91	80	73
Life Table Tests	P=0.006	P=0.015	P=0.011
Incidental Tumor Tests	P=0.104	P=0.362	P=0.213
Stage (c)			
1	1	3	6
2	4	5	3
3	5	5	8

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of leukemia at study laboratory (mean ± SD): 32/150 (21% ± 10%); historical incidence in NTP studies: 361/2,099 (17% ± 9%)
(c) Number of animals with the indicated stage

Tongue and Palate: Squamous cell papillomas of the tongue were increased in chemically exposed female rats (vehicle control, 0/50; low dose, 1/50; high dose, 3/50) (Figure 5). A squamous cell papilloma of the palate was seen in one vehicle control female. When squamous cell neoplasms of the tongue and palate are combined, the incidences in chemically exposed female rats are not significantly increased compared with that in vehicle controls (1/50; 1/50; 3/50). The incidences of squamous cell papillomas or carcinomas (combined) of the tongue were not increased in chemically exposed male rats (1/50; 2/50; 0/50).

Pituitary Gland: Adenomas occurred in male rats with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the vehicle controls (vehicle control, 18/48; low dose, 16/48; high dose, 22/45); however, the increase in the high dose group was not considered to be indicative of an effect of chemical exposure because of the high and variable incidence of these neoplasms in corn oil vehicle control F344/N rats (Table A4c) and the absence of a corresponding increase in pituitary hyperplasia (12/48; 8/48; 14/45). The incidences of pituitary neoplasms decreased in high dose female rats (20/49; 21/50; 12/48).

Pancreatic Islets: Metaplasia occurred at increased ($P<0.01$) incidences in high dose female rats (vehicle control, 0/50; low dose, 1/50; high dose, 11/49). This lesion consisted of scattered aggregates of well-differentiated hepatocytes, usually adjacent to the pancreatic islets (Figure 6). No evidence of degeneration, necrosis, or other histologic changes was apparent in the pancreatic acini or islets in association with the metaplastic changes.

Forestomach: Chronic inflammation, ulcers, and epithelial hyperplasia were observed at increased incidences in chemically exposed male rats (Table 10).

Mammary Gland: Fibroadenomas occurred in three high dose male rats.

TABLE 10. NUMBERS OF RATS WITH FORESTOMACH LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN

Lesion	Male (a)			Female (b)		
	Vehicle Control	30 mg/kg	60 mg/kg	Vehicle Control	60 mg/kg	120 mg/kg
Number examined	50	50	49	50	13	49
Chronic inflammation	1	**11	6	0	1	1
Ulcers	1	5	*8	0	2	1
Epithelial hyperplasia	9	15	*18	0	3	3
Squamous cell papilloma	1	0	1	0	0	0
Squamous cell carcinoma	0	0	0	0	0	1

(a) Historical incidence of papillomas or carcinomas (combined) at study laboratory: 0/138 ; historical incidence in NTP studies (mean ± SD): 7/2,072 (0.3% ± 0.8%)
(b) Historical incidence of papillomas or carcinomas (combined) at study laboratory : 0/148; historical incidence in NTP studies (mean ± SD): 9/2,085 (0.4% ± 1%)
*$P<0.05$ vs. the vehicle controls
**$P<0.01$ vs. the vehicle controls

FOURTEEN-DAY STUDIES

Four male mice and five female mice died before the end of the studies; a sixth female was missing (Table 11). Gross evidence of gavage error (oily fluid in the pleural cavity) was present in all mice that died early. Final mean body weights of chemically exposed mice were similar to those of controls. No histologic lesions attributable to chemical exposure were observed in the three mice of each sex in the high dose groups which were examined at study termination.

THIRTEEN-WEEK STUDIES

Seven of 10 males and 3/10 females that received 500 mg/kg and 1/10 males that received 250 mg/kg died before the end of the studies (Table 12). Gross evidence of gavage error was seen in three males and one female in the 500 mg/kg groups which died on day 1. The final mean body weight of male mice that received 500 mg/kg was 13% lower than that of vehicle controls; final mean body weights of other groups of chemically exposed mice were similar to those of vehicle controls. Reduced motor activity and salivation after dosing were observed in all groups of chemically exposed mice but were more frequent in mice that received the highest dose.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF BENZOFURAN

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	5/5	24.6 ± 0.7	29.1 ± 0.8	+ 4.5 ± 1.3	
15.63	5/5	25.2 ± 0.6	27.9 ± 0.7	+ 2.7 ± 0.5	95.9
31.25	5/5	27.5 ± 0.5	26.3 ± 0.6	− 1.2 ± 0.5	90.4
62.5	(e) 4/5	25.6 ± 0.8	27.5 ± 1.1	+ 1.8 ± 0.5	94.5
125	(f) 3/5	26.5 ± 1.5	28.3 ± 2.4	+ 1.2 ± 1.7	97.3
250	(g) 4/5	27.1 ± 0.8	28.5 ± 0.8	+ 1.3 ± 1.1	97.9
FEMALE					
(d) 0	5/5	20.8 ± 0.5	23.7 ± 0.5	+ 2.9 ± 0.4	
15.63	(h) 4/5	20.1 ± 0.7	21.9 ± 0.8	+ 1.5 ± 0.3	92.4
31.25	(g) 4/5	20.4 ± 0.7	23.4 ± 1.1	+ 2.7 ± 0.6	98.7
62.5	(i) 3/5	20.9 ± 0.6	23.0 ± 1.5	+ 2.2 ± 0.3	97.0
125	(g) 4/5	20.3 ± 0.7	21.9 ± 0.8	+ 1.6 ± 0.3	92.4
250	(j) 4/5	21.0 ± 0.5	24.8 ± 0.8	+ 3.5 ± 1.2	104.6

(a) Number surviving/number initially in the group; all early deaths were probably gavage related.
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Controls were untreated.
(e) Day of death: 8
(f) Day of death: 6,8
(g) Day of death: 5
(h) Animal missing
(i) Day of death: 6,7
(j) Day of death: 15

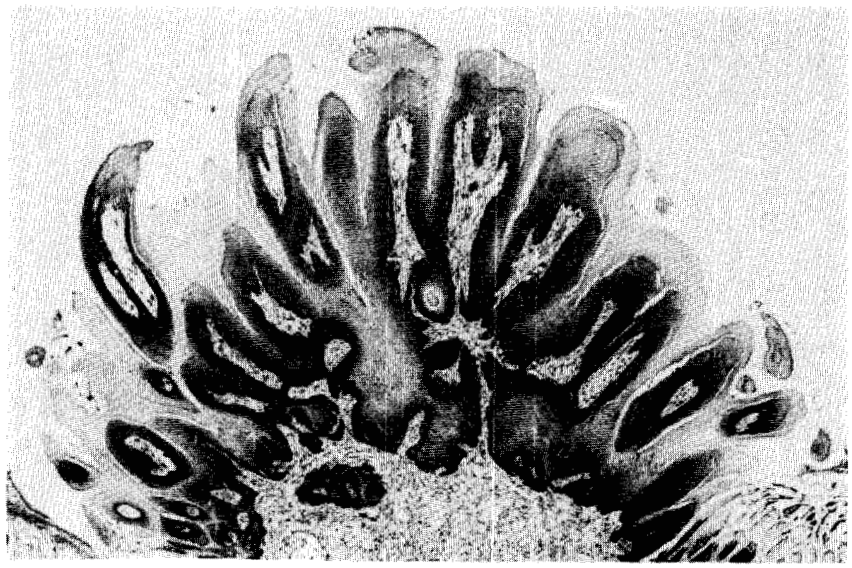


Figure 5. Squamous cell papilloma of the oral mucosa in low dose female rat no. 22.

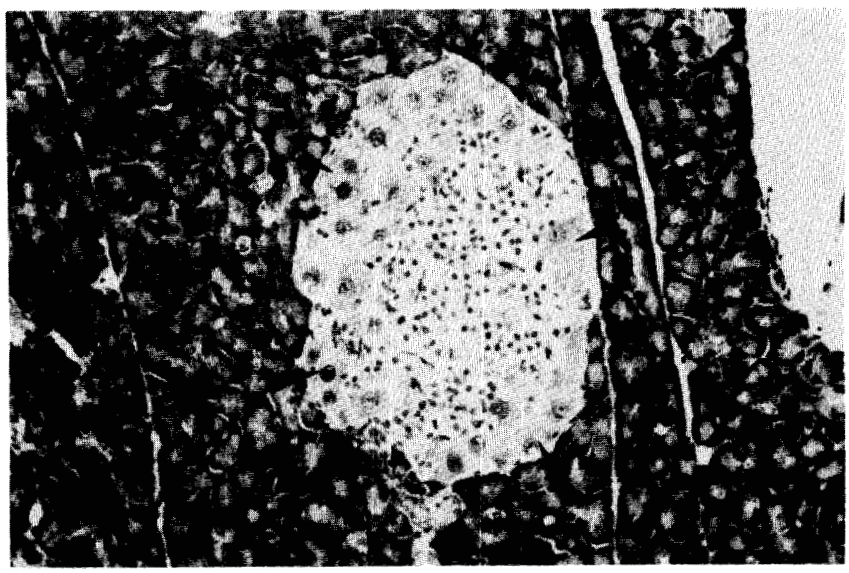


Figure 6. Hepatocyte metaplasia at the periphery of an islet of Langerhans in the pancreas.

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BENZOFURAN

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	25.2 ± 0.8	35.9 ± 0.5	10.7 ± 0.6	
31.25	10/10	25.1 ± 0.3	32.4 ± 1.5	7.3 ± 1.4	90.3
62.5	(d) 9/10	24.2 ± 1.0	36.3 ± 0.5	12.4 ± 1.1	101.1
125	10/10	24.7 ± 0.7	37.7 ± 1.0	13.0 ± 0.8	105.0
250	(e) 9/10	26.0 ± 0.5	34.7 ± 0.5	8.7 ± 0.5	96.7
500	(f) 3/10	23.9 ± 0.7	31.4 ± 0.3	6.2 ± 0.4	87.5
FEMALE					
0	10/10	20.4 ± 0.3	27.1 ± 0.5	6.7 ± 0.5	
31.25	10/10	20.0 ± 0.4	28.0 ± 0.6	0.0 ± 0.3	103.3
62.5	10/10	19.4 ± 0.5	26.9 ± 0.8	7.5 ± 0.5	99.3
125	10/10	20.0 ± 0.4	28.0 ± 0.4	0.0 ± 0.4	103.3
250	10/10	20.3 ± 0.2	26.4 ± 0.5	6.1 ± 0.4	97.4
500	(g) 7/10	21.5 ± 0.5	26.3 ± 0.5	4.6 ± 0.3	97.0

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 13
(e) Week of death: 12
(f) Week of death: all 1
(g) Week of death: 1,1,3

Nephrosis occurred in 7/10 male mice that received 250 mg/kg. The lesions were characterized by the presence of tubular cell necrosis, inflammation, fibrosis, regeneration, and focal mineralization. No histologic lesions were associated with chemical exposure in male mice that received doses lower than 250 mg/kg or in female mice.

Dose Selection Rationale: Because of reduced survival that occurred in males and females that received 500 mg/kg and the nephrotoxicity observed in males that received 250 mg/kg, doses selected for mice for the 2-year studies were 60 and 120 mg/kg benzofuran in corn oil for males and 120 and 240 mg/kg benzofuran for females, administered by gavage 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of low dose male mice were 5%-11% lower than those of vehicle controls between week 20 and 89 (Table 13 and Figure 7). Mean body weights of high dose male mice were generally within 5% of those of vehicle controls. Mean body weights of high dose female mice were 8%-35% lower than those of vehicle controls after week 20. Mean body weights of low dose female mice were 11%-26% lower than those of vehicle controls after week 40.

TABLE 13. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of veh. controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of veh. controls)	High Dose No. of Survivors
MALE				**60 mg/kg**			**120 mg/kg**	
0	26.4	50	25.2	95	50	25.9	98	50
1	27.0	50	25.3	94	50	27.4	101	50
2	27.5	50	25.9	94	50	26.9	98	50
3	28.4	50	28.3	100	50	28.7	101	50
4	27.8	50	28.3	102	50	27.8	100	50
5	27.8	50	27.4	99	50	27.9	100	50
6	28.5	50	28.8	101	50	29.6	104	50
7	31.1	50	30.6	98	49	31.0	100	50
8	31.6	50	31.5	100	49	31.8	101	50
9	31.5	50	31.6	100	49	32.0	102	50
10	32.3	50	30.9	96	49	31.3	97	50
11	33.5	50	37.0	110	49	34.4	103	50
12	33.2	50	34.3	103	49	34.1	103	50
16	33.5	49	33.5	100	49	33.7	101	49
20	37.9	49	33.8	89	45	35.7	94	48
24	38.3	49	35.6	93	39	37.9	99	48
29	41.3	49	37.6	91	39	39.0	94	48
32	42.9	49	39.1	91	39	40.2	94	48
36	42.2	49	38.8	92	37	39.5	94	47
40	42.9	49	39.8	93	37	40.1	93	47
44	42.7	48	40.3	94	37	41.4	97	46
48	43.2	48	40.6	94	37	41.0	95	46
52	43.9	48	41.9	95	37	42.6	97	45
56	44.5	48	41.9	94	37	43.2	97	45
60	44.9	48	42.0	94	37	43.6	97	45
64	45.8	48	42.2	92	35	43.7	95	45
68	46.1	48	42.1	91	35	42.6	92	45
72	45.8	48	41.7	91	35	43.9	96	42
77	45.0	48	40.5	90	35	43.1	96	41
81	45.4	47	41.4	91	33	44.0	97	40
89	44.5	44	42.0	94	27	40.8	92	39
93	43.0	42	41.7	97	25	41.7	97	35
97	42.6	40	41.7	98	21	39.8	93	35
101	40.6	34	41.6	102	20	38.8	96	31
FEMALE				**120 mg/kg**			**240 mg/kg**	
0	19.6	50	20.2	103	50	20.0	102	50
1	20.0	50	20.0	100	50	19.7	99	50
2	19.6	50	21.3	109	50	20.6	105	50
3	22.7	50	21.2	93	50	20.4	90	50
4	21.8	50	22.9	105	48	21.8	100	50
5	21.9	50	22.7	104	48	22.3	102	50
6	22.6	50	24.3	108	48	24.0	106	50
7	22.7	49	24.7	109	47	22.9	101	50
8	22.1	49	24.2	110	47	22.7	103	50
9	22.8	49	24.7	108	46	23.5	103	50
10	25.4	49	25.5	100	46	24.5	96	50
11	26.8	49	27.8	104	46	26.3	98	50
12	28.0	49	26.0	93	46	27.3	98	50
16	25.9	49	25.6	99	46	24.4	94	49
20	28.2	49	27.7	98	45	25.9	92	49
24	29.3	49	27.6	94	45	25.3	86	49
29	30.9	49	28.1	91	45	25.4	82	48
32	32.0	49	29.5	92	45	25.6	80	47
36	31.1	49	29.1	94	45	26.0	84	47
40	34.5	49	29.6	86	45	26.5	77	47
44	34.4	49	30.0	87	45	26.1	76	47
48	35.3	49	30.5	86	45	26.9	76	47
52	36.3	49	31.0	85	45	26.5	73	47
56	36.4	49	31.8	87	45	26.8	74	47
60	37.4	49	31.7	85	45	27.0	72	47
64	37.4	49	32.1	86	44	27.2	73	46
68	39.5	49	32.7	83	44	27.7	70	46
72	39.5	47	32.6	83	44	27.4	69	44
77	38.2	46	34.0	89	40	28.8	75	42
81	41.4	45	36.3	88	36	29.3	71	39
89	43.8	45	32.4	74	30	28.5	65	37
93	39.5	43	34.0	86	26	31.0	78	33
97	42.4	41	34.3	81	22	30.9	73	23
101	41.1	41	33.9	82	19	30.2	73	21

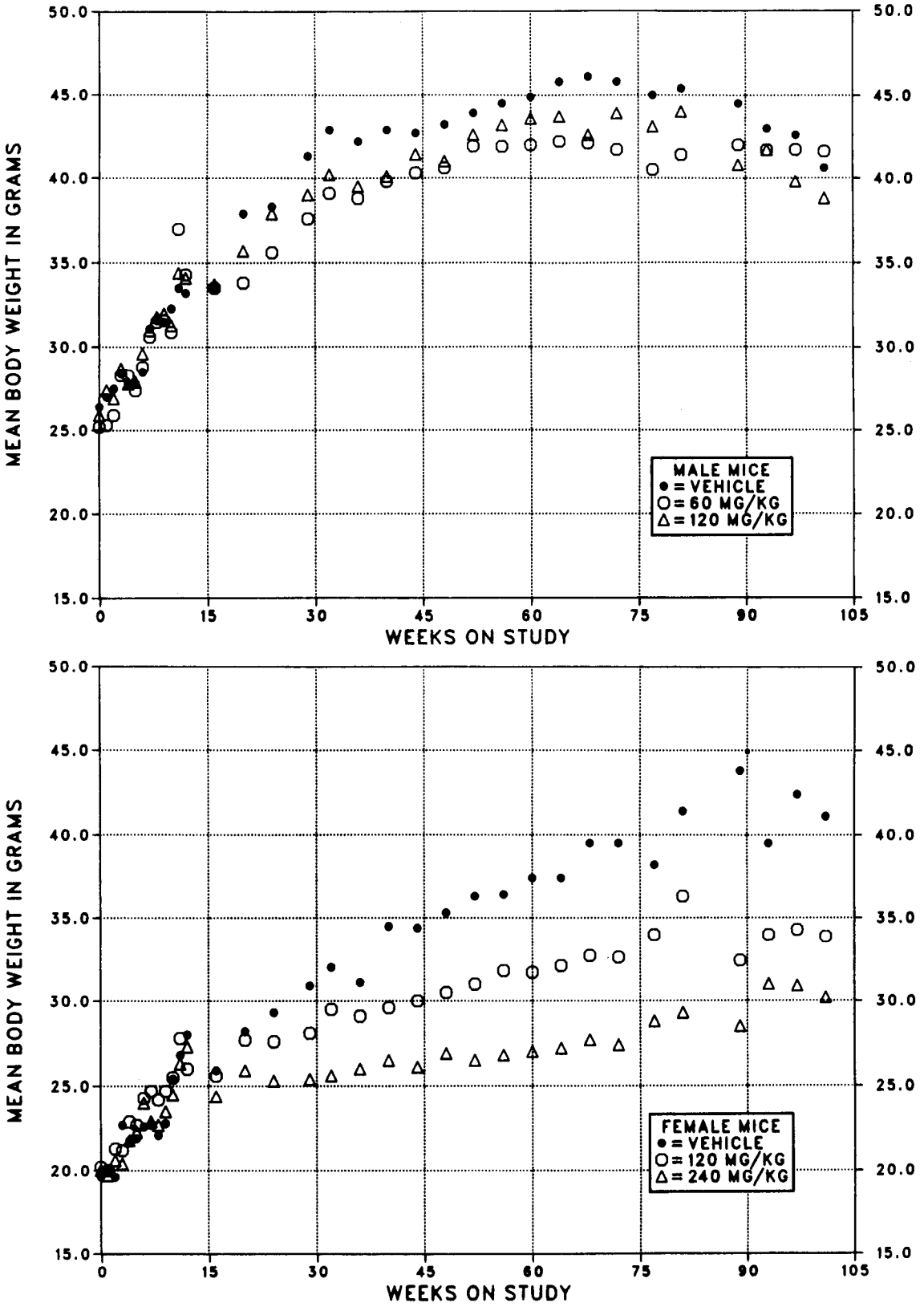


FIGURE 7. GROWTH CURVES FOR MICE ADMINISTERED BENZOFURAN IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered benzofuran at the doses used in these studies and for vehicle controls are shown in Table 14 and in the Kaplan and Meier curves in Figure 8. The survival of the low (after week 89) and high (after week 96) dose groups of female mice was significantly lower than that of the vehicle controls. No other significant differences in survival were observed between any groups of either sex. Ten low dose male mice died at weeks 20-21 as a consequence of a fourfold overdose; these animals were censored from the analysis of survival.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, forestomach, lung, nasal cavity, and ovary.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively. Male mice dying before week 22 were excluded from the statistical analyses of neoplastic and nonneoplastic lesions because they had not survived sufficiently long to be at risk for developing tumors.

TABLE 14. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
MALE (a)				
Animals initially in study	50	50	50	
Natural deaths	8	10	(b) 16	
Moribund kills	8	7	4	
Animals surviving until study termination	33	20	28	
Killed accidentally	1	13	3	
Survival P values (c)	0.426	0.197	0.477	
FEMALE (a)				
Animals initially in study	50		50	50
Natural deaths	12		23	20
Moribund kills	1		4	7
Animals surviving until study termination	37		19	21
Killed accidentally	0		4	2
Survival P values (c)	0.006		0.002	0.005

(a) Termination period: week 104
(b) One animal in this group died during the termination period and was combined, for statistical purposes, with those killed at termination.
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

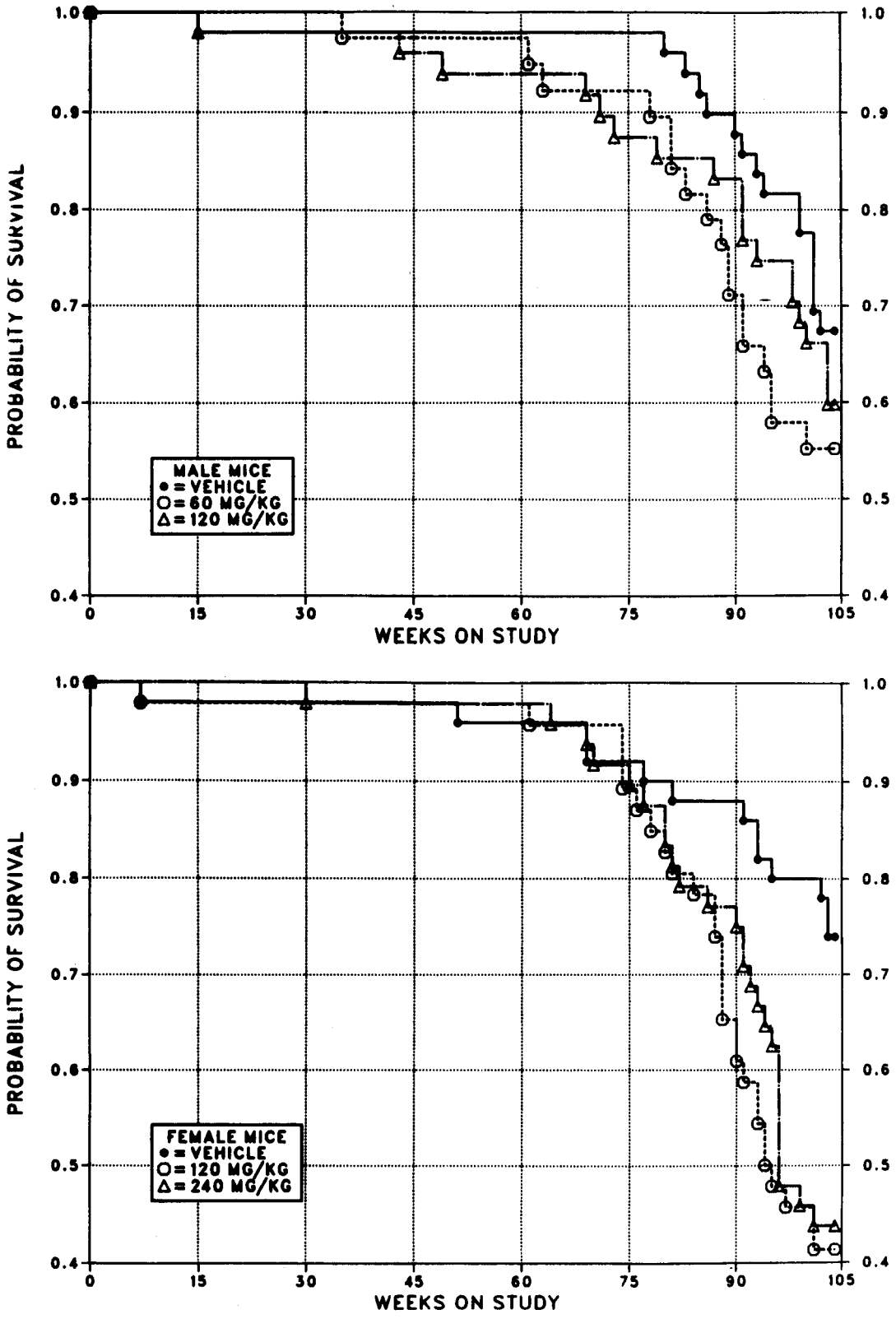


FIGURE 8. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED BENZOFURAN IN CORN OIL BY GAVAGE FOR TWO YEARS

Liver: Syncytial alteration, characterized by randomly scattered hepatocytes containing three or more nuclei, occurred at increased incidences in chemically exposed male mice (male: vehicle control, 4/49; low dose, 18/39; high dose, 36/48; female: 1/50; 0/48; 2/47) (Figure 9). The incidences of hepatocellular adenomas were significantly increased in chemically exposed mice (Table 15). The incidences of hepatocellular carcinomas were not increased, but the incidences of hepatoblastomas were significantly increased in males and followed a positive trend in females. The incidences of hepatocellular adenomas, hepatocellular carcinomas, or hepatoblastomas (combined) were significantly increased in chemically exposed mice.

TABLE 15. LIVER TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN (a)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
MALE (b)				
Hepatocellular Adenoma				
Overall Rates	4/49 (8%)	24/39 (62%)	34/48 (71%)	
Terminal Rates	4/33 (12%)	16/20 (80%)	22/28 (79%)	
Week of First Observation	104	81	71	
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001	
Hepatocellular Carcinoma				
Overall Rates	9/49 (18%)	8/39 (21%)	9/48 (19%)	
Hepatoblastoma				
Overall Rates	0/49 (0%)	3/39 (8%)	18/48 (38%)	
Terminal Rates	0/33 (0%)	1/20 (5%)	12/28 (43%)	
Week of First Observation		78	87	
Incidental Tumor Tests	P<0.001	P=0.083	P<0.001	
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma (c)				
Overall Rates	12/49 (24%)	31/39 (80%)	40/48 (83%)	
Terminal Rates	6/33 (18%)	19/20 (95%)	26/28 (93%)	
Week of First Observation	80	78	71	
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001	
FEMALE				
Hepatocellular Adenoma				
Overall Rates	1/50 (2%)		22/48 (46%)	21/47 (45%)
Terminal Rates	1/37 (3%)		17/19 (89%)	13/21 (62%)
Week of First Observation	104		74	91
Incidental Tumor Tests	P<0.001		P<0.001	P<0.001
Hepatocellular Carcinoma				
Overall Rates	3/50 (6%)		3/48 (6%)	1/47 (2%)
Hepatoblastoma (d)				
Overall Rates	0/50 (6%)		1/48 (2%)	2/47 (4%)
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma (e)				
Overall Rates	4/50 (8%)		25/48 (52%)	22/47 (47%)
Terminal Rates	3/37 (8%)		17/19 (89%)	14/21 (67%)
Week of First Observation	103		74	91
Incidental Tumor Tests	P<0.001		P<0.001	P<0.001

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Only male mice that survived more than 21 weeks on study are included.
(c) Historical incidence at study laboratory (mean ± SD): 39/150 (26% ± 11%); historical incidence in NTP studies: 688/2,084 (33% ± 9%)
(d) All hepatoblastomas were observed in animals that had hepatocellular adenomas.
(e) Historical incidence at study laboratory (mean ± SD): 8/149 (5% ± 5%); historical incidence in NTP studies: 156/2,088 (7% ± 5%)

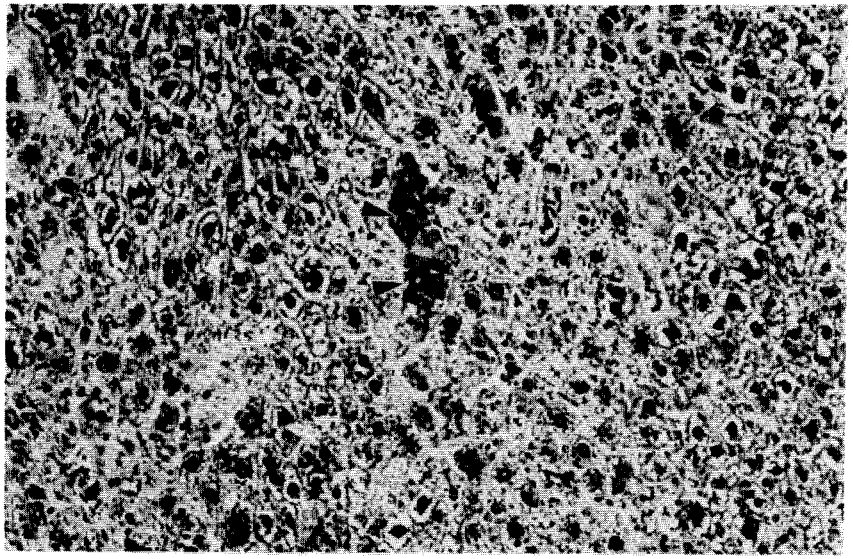


Figure 9. Hepatocellular syncytial alteration in liver of high dose male mouse no. 10.

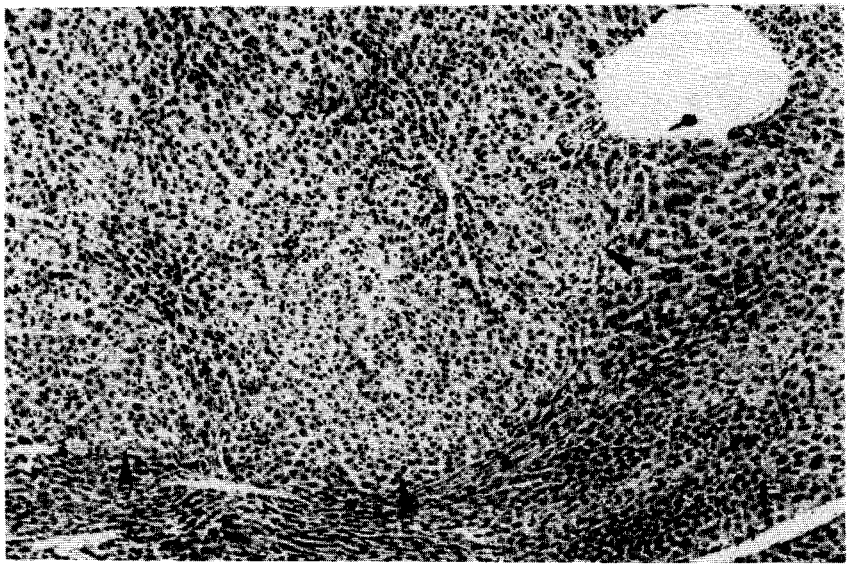


Figure 10. Hepatocellular adenoma in liver of low dose male mouse no. 30. The margin of the neoplasm is denoted by arrows.

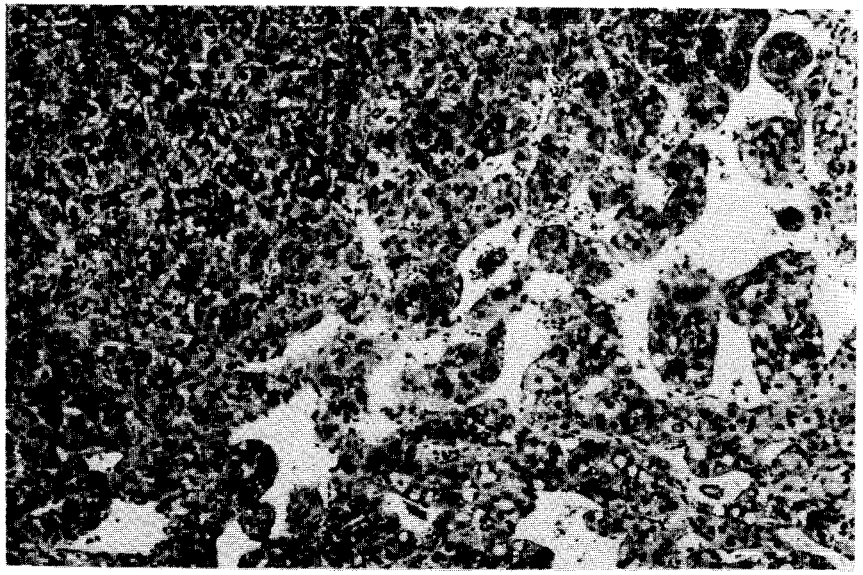


Figure 11. Hepatocellular carcinoma in liver of high dose male mouse no. 44. Note the trabecular pattern of growth.

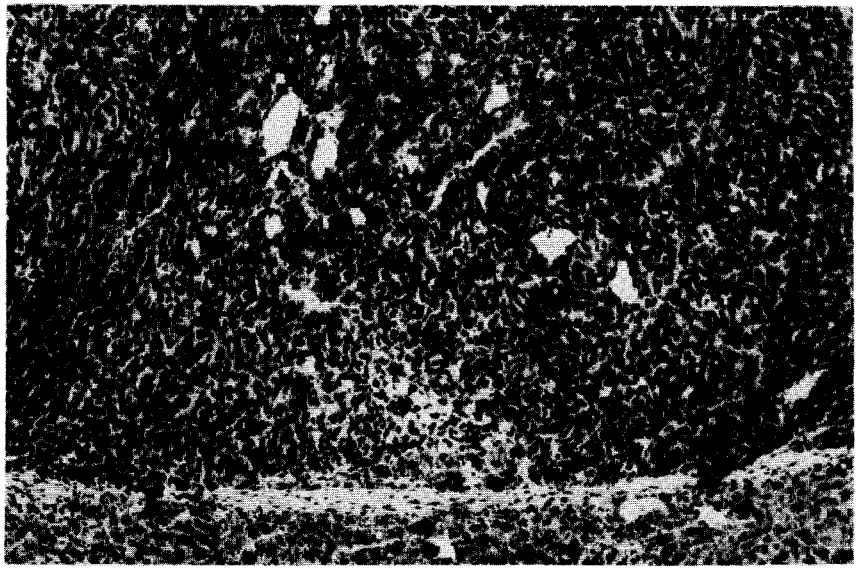


Figure 12. Hepatoblastoma in liver of high dose male mouse no. 26, consisting of solid sheets of undifferentiated cells with scant cytoplasm and large oval-to-elongated hyperchromatic nuclei. Compare with normal hepatocytes at the bottom of the photomicrograph.

Hepatocellular adenomas were circumscribed expansile masses lacking clearly defined lobular architecture and were composed of irregular cords and/or clumps of well-differentiated hepatocytes (Figure 10). Hepatocellular carcinomas were expansile, well-demarcated masses composed of dense sheets, thick (greater than three cell layers) trabecular and/or glandlike structures of hepatocytes with abundant cytoplasm, large vesicular nuclei, and numerous mitotic figures (Figure 11).

Hepatoblastomas are uncommon neoplasms in B6C3F$_1$ mice. The histologic appearance of hepatoblastomas has been described by Turusov et al. (1973) and Nonoyama et al. (1988). The neoplasms observed in the current studies compressed or replaced adjacent liver tissue and were composed of densely packed sheets of small cells with indistinct borders, scant basophilic cytoplasm, and hyperchromatic nuclei (Figure 12). Numerous dilated thin-walled vascular channels were also present.

Forestomach: Epithelial hyperplasia was observed at increased incidences in high dose males and in chemically exposed females (Table 16). The incidence of squamous cell papillomas increased in female mice that received 120 mg/kg. The incidences of squamous cell papillomas or carcinomas (combined) were significantly increased in male mice that received 60 or 120 mg/kg and in female mice that received 120 mg/kg (Figures 13 and 14). In five animals, the carcinomas were invasive into adjacent organs, and, in three animals, they had metastasized.

Lung: Epithelial hyperplasia of the bronchioles, characterized by proliferation of the respiratory epithelium of terminal bronchioles which often extended into alveolar ducts, occurred at increased incidences in chemically exposed mice (Table 17). The incidences of alveolar/bronchiolar adenomas and of alveolar/bronchiolar adenomas or carcinomas (combined) showed significant positive trends and were significantly increased in female mice that received 120 or 240 mg/kg and marginally increased in male mice that received 120 mg/kg. The incidence of alveolar/bronchiolar carcinomas was significantly increased in female mice that received 120 mg/kg.

Alveolar/bronchiolar adenomas were well-circumscribed nodules that compressed adjacent parenchyma and consisted of tubular, papillary, or ribbon-like arrangements of columnar epithelial cells. Alveolar/bronchiolar carcinomas were characterized as large, expansile nodular masses composed of irregular papillary projections of low-to-high columnar epithelium and/or densely packed sheets of pleomorphic cells with indistinct borders, a high nuclear to cytoplasmic ratio, and frequent mitoses.

Nasal Cavity: Acute and chronic inflammation of the nasal mucosa occurred in chemically exposed and vehicle control mice. Associated with the inflammation were epithelial hyperplasia and metaplasia (characterized by focal replacement of olfactory epithelium by ciliated respiratory epithelium) of the respiratory region of the nose (metaplasia--male: vehicle control, 0/49; low dose, 1/39; high dose, 11/48; female: 5/50; 20/45; 43/47). Metaplasia of the olfactory epithelium and other nonneoplastic lesions were considered secondary to the presence of foreign material (corn oil, hair, particles of feed or bedding) that had become lodged in the nasal cavity. Since the inflammation was more extensive in high dose animals, especially females, exposure at the highest dose of benzofuran may have exacerbated the inflammation.

Ovary: Papillary cystadenomas were seen in 2/31 low dose female mice. The mean historical incidence of ovarian papillary neoplasms in corn oil vehicle control female B6C3F$_1$ mice is 6/1,980 (0.3%).

TABLE 16. FORESTOMACH LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN (a)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
MALE (b)				
Epithelial Hyperplasia				
Overall Rates (c)	16/49 (33%)	13/39 (33%)	24/48 (48%)	
Squamous Cell Papilloma				
Overall Rates (d)	2/49 (4%)	7/39 (18%)	10/48 (21%)	
Terminal Rates	2/33 (6%)	5/20 (25%)	8/28 (29%)	
Week of First Observation	104	91	98	
Incidental Tumor Tests	P=0.006	P=0.018	P=0.007	
Squamous Cell Carcinoma				
Overall Rates (d)	0/49 (0%)	4/39 (10%)	3/48 (6%)	
Terminal Rates	0/33 (0%)	1/20 (5%)	1/28 (4%)	
Week of First Observation		88	33	
Incidental Tumor Tests	P=0.122	P=0.050	P=0.161	
Squamous Cell Papilloma or Carcinoma (e)				
Overall Rates (d)	2/49 (4%)	11/39 (28%)	13/48 (27%)	
Terminal Rates	2/33 (6%)	6/20 (30%)	9/28 (32%)	
Week of First Observation	104	88	33	
Incidental Tumor Tests	P=0.002	P=0.001	P=0.001	
FEMALE				
Epithelial Hyperplasia				
Overall Rates (c)	7/50 (14%)		**19/48 (40%)	13/47 (28%)
Squamous Cell Papilloma				
Overall Rates (d)	2/50 (4%)		8/50 (16%)	5/50 (10%)
Terminal Rates	1/37 (3%)		4/19 (21%)	4/21 (19%)
Week of First Observation	102		76	99
Incidental Tumor Tests	P=0.157		P=0.035	P=0.133
Squamous Cell Carcinoma				
Overall Rates (d)	0/50 (0%)		1/50 (2%)	1/50 (2%)
Squamous Cell Papilloma or Carcinoma (f)				
Overall Rates (d)	2/50 (4%)		9/50 (18%)	5/50 (10%)
Terminal Rates	1/37 (3%)		5/19 (26%)	4/21 (19%)
Week of First Observation	102		76	99
Incidental Tumor Tests	P=0.148		P=0.015	P=0.133

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Only male mice that survived more than 21 weeks on study are included.
(c) Number of animals with lesions/number of animals examined microscopically
(d) Number of animals with lesions/number of animals examined grossly
(e) Historical incidence at study laboratory (mean ± SD): 6/146 (4% ± 4%); historical incidence in NTP studies: 39/2,033 (2% ± 3%)
(f) Historical incidence at study laboratory (mean ± SD): 7/141 (5% ± 6%); historical incidence in NTP studies: 33/2,047 (2% ± 3%)
**P<0.01 vs. the vehicle controls

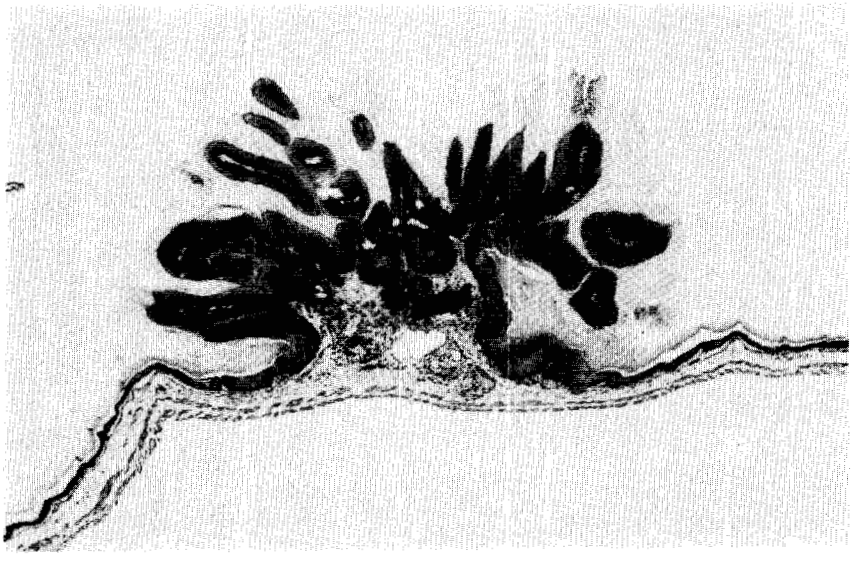


Figure 13. Squamous cell papilloma in the forestomach of high dose male mouse no. 11.

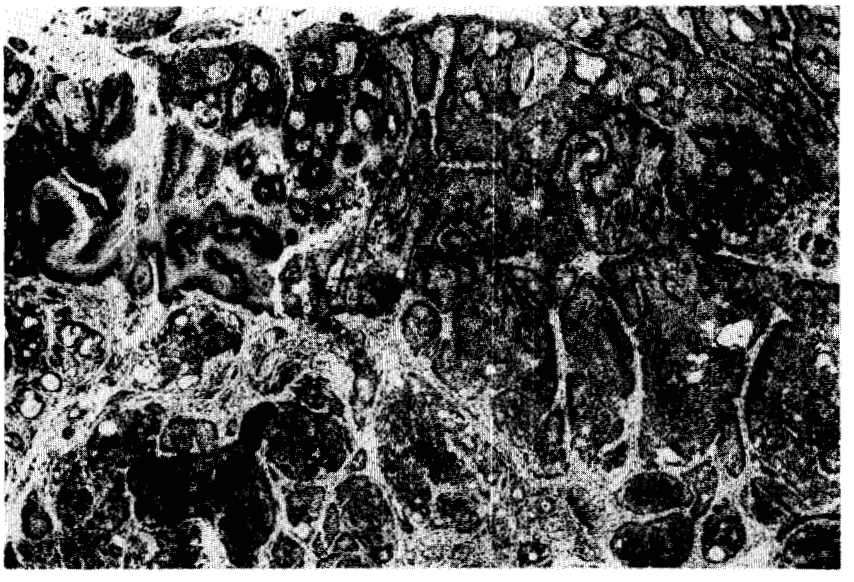


Figure 14. Squamous cell carcinoma in the forestomach of high dose male mouse no. 2. Note the thick, branching cords of squamous epithelium.

TABLE 17. LUNG LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN (a)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
MALE (b)				
Bronchiolar Epithelial Hyperplasia				
Overall Rates	3/49 (6%)	**11/39 (28%)	**14/48 (29%)	
Alveolar/Bronchiolar Adenoma				
Overall Rates	4/49 (8%)	7/39 (18%)	15/48 (31%)	
Terminal Rates	4/33 (12%)	3/20 (15%)	10/28 (36%)	
Week of First Observation	104	81	69	
Incidental Tumor Tests	P=0.002	P=0.101	P=0.003	
Alveolar/Bronchiolar Carcinoma				
Overall Rates	7/49 (14%)	3/39 (8%)	5/48 (10%)	
Terminal Rates	4/33 (12%)	2/20 (10%)	2/28 (7%)	
Week of First Observation	85	100	71	
Incidental Tumor Tests	P=0.262N	P=0.382N	P=0.228N	
Alveolar/Bronchiolar Adenoma or Carcinoma (c)				
Overall Rates	10/49 (20%)	9/39 (23%)	19/48 (40%)	
Terminal Rates	7/33 (21%)	4/20 (20%)	11/28 (39%)	
Week of First Observation	85	81	69	
Incidental Tumor Tests	P=0.022	P=0.342	P=0.053	
FEMALE				
Bronchiolar Epithelial Hyperplasia				
Overall Rates	1/50 (2%)		**22/48 (46%)	**34/47 (72%)
Alveolar/Bronchiolar Adenoma				
Overall Rates	1/50 (2%)		5/48 (10%)	13/47 (28%)
Terminal Rates	1/37 (3%)		3/19 (16%)	6/21 (29%)
Week of First Observation	104		94	82
Incidental Tumor Tests	P<0.001		P=0.040	P<0.001
Alveolar/Bronchiolar Carcinoma				
Overall Rates	1/50 (2%)		4/48 (8%)	3/47 (6%)
Terminal Rates	1/37 (3%)		4/19 (21%)	1/21 (5%)
Week of First Observation	104		104	86
Incidental Tumor Tests	P=0.153		P=0.038	P=0.350
Alveolar/Bronchiolar Adenoma or Carcinoma (d)				
Overall Rates	2/50 (4%)		9/48 (19%)	14/47 (30%)
Terminal Rates	2/37 (5%)		7/19 (37%)	6/21 (29%)
Week of First Observation	104		94	82
Incidental Tumor Tests	P<0.001		P=0.002	P=0.002

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Only male mice that survived more than 21 weeks on study are included.
(c) Historical incidence at study laboratory (mean ± SD): 23/150 (15% ± 4%); historical incidence in NTP studies: 349/2,084 (17% ± 7%)
(d) Historical incidence at study laboratory (mean ± SD): 10/149 (7% ± 2%); historical incidence in NTP studies: 131/2,082 (6% ± 3%)
**P<0.01 vs. the vehicle controls

Benzofuran was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of exogenous metabolic activation. Benzofuran induced trifluorothymidine resistance in mouse L5178Y lymphoma cells treated in the absence of metabolic activation; this assay was not conducted with activation. Benzofuran induced sister chromatid exchanges but not chromosomal aberrations in Chinese hamster ovary cells in the presence and absence of activation.

The experimental procedures and results are presented in Appendix H.

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Benzofuran is used in the manufacture of resins present in a number of consumer products and in certain adhesives approved for use in food packaging. Substituted benzofurans are also present in several pharmaceuticals. Because of the potential for human exposure suggested by these uses, toxicology and carcinogenesis studies were conducted to evaluate the potential hazards associated with exposure to benzofuran. During the current studies, benzofuran was administered by gavage to provide systemic exposure and because of the importance of oral exposure for humans.

During the 13-week studies, male rats and male mice exhibited a greater sensitivity to benzofuran toxicity than did females. Reduction of final mean body weights and the severity of nephropathy were greater in male rats than in females receiving the same doses. Slight survival differences were observed between male and female mice in the 13-week studies; however, nephrosis occurred in male mice that received 250 mg/kg or more but was not present in lower dose males or in females. Because of these sex differences, doses selected for male rats and mice for the 2-year studies were lower than those selected for females.

In the 2-year studies, chemically exposed male rats had lower mean body weights and significantly reduced survival after week 89, but mean body weights and survival of female rats were relatively unaffected by chemical exposure. In mice, however, exposure to benzofuran for 2 years caused a marked reduction in survival in females, whereas body weights of chemically exposed males were only slightly lower than those of vehicle controls and survival was unaffected.

Nonneoplastic lesions of the kidney were present in both male and female rats exposed to benzofuran for 2 years. In males, the severity of nephropathy was increased; lesions characteristic of renal secondary hyperparathyroidism, including parathyroid hyperplasia, fibrous osteodystrophy, and mineralization of the pulmonary artery, were also increased. These nonneoplastic lesions occur as a result of disruption of calcium and phosphorus homeostasis associated with loss of renal function. The incidences of nephropathy were also increased in chemically exposed female rats, although the severity was less than that observed in males.

No renal neoplasms were observed in male rats; however, atypical tubular cell hyperplasia and tubular cell adenocarcinomas were present at increased incidences in chemically exposed female rats. Tubular cell adenocarcinomas are uncommon in female rats, having never been observed in 2,094 corn oil vehicle control female F344/N rats in the 2-year gavage studies included in the National Toxicology Program (NTP) data base (Table B4a).

The atypical tubular cell hyperplasia observed in the current studies closely resembled renal oncocytomas that have been reported in aging untreated control Sprague Dawley rats but are uncommon in F344/N rats, especially females. Renal oncocytomas have been induced at high incidences in Sprague Dawley rats exposed to *N*-nitrosomorpholine; they are generally slow growing, and no reports have documented invasive growth or metastasis. Studies of the progressive development of oncocytomas in rats exposed to *N*-nitrosomorpholine indicate that these neoplasms arise from the epithelial cells lining the distal kidney tubule, in contrast to tubular cell adenocarcinomas, which generally are thought to develop in the proximal tubules (Bannasch et al., 1986; Nogueira and Bannasch, 1988). Therefore, the oncocytomas and adenocarcinomas do not appear to be part of the same morphologic continuum.

The dose-related increases in the incidences of renal neoplasms and atypical tubular cell hyperplasia are considered to be associated with benzofuran. These lesions were present only in chemically exposed female rats, and although it might be argued that the increased incidences of nephropathy might have contributed to the development of these neoplasms, renal neoplasms were not found in male rats receiving comparable doses of benzofuran in the presence of much more severe nephropathy. However, the overall magnitude of response was not considered strong enough to constitute clear evidence of carcinogenic activity. The atypical tubular cell hyperplasia was judged to be hyperplastic rather than neoplastic by the NTP Pathology Working Group. There was no hyperplasia of the

proximal tubule epithelium supporting the adenocarcinomas. Therefore, these results were judged to constitute some evidence of carcinogenic activity.

Cells resembling normal hepatocytes were present in the pancreatic islets of 1 high dose male rat and in 1 low dose and 11 high dose female rats. Although uncommon in the normal rat pancreas, similar metaplasia has been reported in rats exposed to [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]-acetic acid (Lalwani et al., 1981) or to ciprofibrate (Reddy et al., 1984). In the latter study, rats fed diets containing ciprofibrate for 60 weeks and maintained on control diets for 12 additional weeks had pancreatic hepatocytes that were morphologically identical to normal hepatocytes. Moreover, ciprofibrate, a hypolipidemic peroxisome proliferator, induced peroxisomes both in normal liver hepatocytes and in the pancreatic hepatocytes. Although the pancreatic metaplasia was induced by chemical exposure, it did not appear to involve neoplastic transformation but rather represented transdifferentiation of one type of terminally differentiated normal cell into another type of terminally differentiated normal cell. A review containing more detailed discussion and references has been published (Rao et al., 1986).

The incidences of neurilemomas in all groups of rats, including vehicle controls, were unusually high in these studies. These tumors were not associated with exposure to benzofuran. Two other studies (*N,N*-dimethylaniline [NTP, 1989] and penicillin VK [NTP, 1988]) conducted concurrently at the same laboratory also had abnormally high incidences of neurilemomas; however, a fourth study at the same laboratory (ampicillin trihydrate [NTP, 1987]), which started earlier than the other three, had very few neurilemomas (Table 18). To obtain a broader perspective on the possible cause of these tumors, the incidence of neurilemomas in rats at all sites was tabulated for all studies started by the NTP between August 1980 and May 1981. This grouping, which includes 41 studies, represents all 2-year studies that were in progress for 6 or fewer months, concurrently with benzofuran. If the underlying cause of the neurilemomas had been related to the animals (rats), the diet, or the bedding available during this period, this effect would have been reflected in this group of studies. The incidence of neurilemomas in rats in all studies started during this time period was similar to the NTP historical control incidence, with the exception of the 2-year studies of benzofuran, *N,N*-dimethylaniline, and penicillin VK. Examination of a more restricted group of studies, those started during the same months as benzofuran, *N,N*-dimethylaniline, and penicillin VK (Table 19), illustrates that the high incidence of neurilemomas is unique to the laboratory that conducted these studies and was not a general problem that affected contemporary NTP studies at other laboratories.

TABLE 18. NUMBERS OF MALE AND FEMALE RATS WITH NEURILEMOMAS AT ALL SITES IN STUDIES CONDUCTED AT THE SPRINGBORN INSTITUTE FOR BIORESEARCH, INC. (a)

Study	Start Date	Control	Low Dose	High Dose
MALE				
Ampicillin trihydrate	8/80	0	0	1
Penicillin VK	12/80	5	3	3
Benzofuran	1/81	18	12	14
N,N-Dimethylaniline	3/81	2	7	7
FEMALE				
Ampicillin trihydrate	8/80	0	1	0
Penicillin VK	12/80	0	4	1
Benzofuran	1/81	7	9	3
N,N-Dimethylaniline	3/81	3	2	2

(a) Groups of 50 rats

TABLE 19. NUMBERS OF MALE AND FEMALE RATS WITH NEURILEMOMAS IN STUDIES STARTING THE SAME MONTH AS PENICILLIN VK, BENZOFURAN, OR *N,N*-DIMETHYLANILINE

Study	Start Date	Control	Low Dose	High Dose
MALE				
Penicillin VK (a)	12/80	5	3	3
C.I. Acid Orange 3 (b)	12/80	0	0	0
Erythromycin stearate (c)	12/80	0	1	2
Rhodamine 6G (b)	12/80	1	1	0
Benzofuran (a)	1/81	18	12	14
Benzyl alcohol (d)	1/81	0	0	0
2-Amino-4-nitrophenol (c)	1/81	1	0	1
Methyl methacrylate (e)	1/81	0	0	0
N,N-Dimethylaniline (a)	3/81	2	7	7
2,4-Dichlorophenol (f)	3/81	0	1	0
4-Hexylresorcinol (c)	3/81	0	0	0
n-Butyl chloride (g)	3/81	0	0	0
Dimethylvinyl chloride (h)	3/81	0	0	0
FEMALE				
Penicillin VK (a)	12/80	0	4	1
C.I. Acid Orange 3 (b)	12/80	0	0	0
Erythromycin stearate (c)	12/80	1	1	0
Rhodamine 6G (b)	12/80	0	0	1
Benzofuran (a)	1/81	7	9	3
Benzyl alcohol (d)	1/81	1	0	0
2-Amino-4-nitrophenol (c)	1/81	2	0	0
Methyl methacrylate (e)	1/81	0	0	0
N,N-Dimethylaniline (a)	3/81	3	2	2
2,4-Dichlorophenol (f)	3/81	0	0	0
4-Hexylresorcinol (c)	3/81	0	0	0
n-Butyl chloride (g)	3/81	0	0	0
Dimethylvinyl chloride (h)	3/81	1	1	0

(a) Studies were conducted at Springborn Institute for Bioresearch, Inc.
(b) Studies were conducted at Southern Research Institute.
(c) Studies were conducted at Physiological Research Laboratories.
(d) Studies were conducted at Microbiological Associates.
(e) Studies were conducted at Battelle Pacific Northwest Laboratories.
(f) Studies were conducted at Battelle Columbus Laboratories.
(g) Studies were conducted at EG&G Mason Research Institute.
(h) Studies were conducted at Litton Bionetics, Inc.

The NIH 07 Rat and Mouse Ration used for the first 4 months of the benzofuran studies contained total nitrosamine concentrations that were tenfold to thirtyfold greater (115-266.2 ppb) than acceptable levels (Appendix F). However, this same batch of feed was used in all NTP studies that were in progress during the period from January through April 1981. Since only the three studies conducted at Springborn Institute for Bioresearch, Inc., had increased incidences of neurilemomas, the increases did not appear to be related to the diet.

A single exposure to methyl(acetoxymethyl)nitrosamine (13 mg/kg) or dimethylnitrosamine (30 mg/kg) has been reported to induce neurilemomas in rats (Haas et al., 1974; Berman et al., 1980). A rat consuming 15 g of feed per day which contained 250 ppb nitrosamines would ingest 3.7 µg nitrosamines per day, or a total of 407 µg nitrosamines for the 110-day period during which the feed was used. For a 220-g male rat (the average body weight of vehicle control male rats during the first 16 weeks of this study), 3.7 µg/day corresponds to 17 µg/kg body weight per day.

In an attempt to determine the cause underlying the increase in neurilemomas, all study records were reviewed in detail. No other chemicals were on study in the same room as benzofuran. Examination of the water analyses and other study records submitted by the study laboratory did not reveal any contaminants, irregularities, or unusual environmental conditions during the period in which these studies were in progress. Sentinel rats and mice in the benzofuran studies exhibited significant murine virus antibody titers throughout the studies, indicating that the barrier or room where the study animals were housed may have been compromised. No evidence in the study records, however, indicated that the use of pesticides or disinfectants was instituted while the studies were in progress. In addition, no reports in the published literature suggested a viral etiology for neurilemomas. Thus, it has not been possible to determine the reason for the unusually high incidences of neurilemomas observed in these studies.

In 2-year studies, *N,N*-dimethylaniline induced the formation of sarcomas or osteosarcomas (combined) in the spleen in rats, whereas penicillin VK exhibited no carcinogenic activity. These results are consistent with the carcinogenic activity of other chemicals of the same respective chemical classes and suggest that whatever factors were involved in producing the increased incidences of neurilemomas probably did not affect the other results of those studies. In the current studies, the kidney was the major target organ in rats, a finding consistent with results of the short-term studies reported here and with the toxicity reported for other furan compounds (McMurtry and Mitchell, 1977).

Liver neoplasms were increased in both male and female mice that received benzofuran during the 2-year studies. In chemically exposed males, there were significant increases in hepatocellular adenomas and hepatoblastomas. In chemically exposed females, the incidences of hepatocellular adenomas were significantly increased, and the incidences of hepatoblastomas were dose related. The incidences of hepatocellular carcinomas were similar in dosed and vehicle control groups of each sex.

Hepatoblastomas are uncommon neoplasms in $B6C3F_1$ mice. The histogenesis of hepatoblastoma cells in mice is still a matter of debate (Nonoyama et al., 1988); however, hepatoblastomas are usually found within, or in close association with, hepatocellular carcinomas. Since the ability of hepatoblastomas to metastasize is not well documented, it is unclear whether they represent a greater hazard than hepatocellular carcinomas. In the current studies, very few metastases of liver neoplasms were observed in benzofuran-exposed mice, indicating that hepatoblastomas did not exhibit a greater tendency to metastasize than did the more common hepatocellular carcinomas.

The significant dose-related increases in liver neoplasms which occurred in chemically exposed mice are considered clear evidence of the carcinogenic activity of benzofuran. This interpretation is consistent with the known bioactivation of furan compounds in the liver and is further supported by recent results suggesting that exposure to two related furan compounds, furan and furfural, may induce liver neoplasms in $B6C3F_1$ mice by induction of certain activating point mutations in the H-*ras* and/or K-*ras* oncogenes (Reynolds et al., 1987; NTP unpublished data).

Squamous cell neoplasms of the forestomach were observed in all groups of chemically exposed mice. Several of the carcinomas were aggressive and invaded adjacent organs and the mesentery. The incidences of squamous cell papillomas or carcinomas (combined) were significantly increased in all groups that received benzofuran (except high dose female mice). Epithelial hyperplasia and inflammation of the forestomach were present both in chemically exposed and in vehicle control mice; however, the absence of a consistent dose-related increase suggests that these nonneoplastic lesions were not related to chemical exposure. Thus, it is unclear to what extent, if any, forestomach hyperplasia, possibly related to the gavage procedure, may have contributed to the development of squamous cell neoplasms.

A dose-related increase in bronchiolar epithelial hyperplasia, alveolar/bronchiolar adenomas,

and alveolar/bronchiolar adenomas or carcinomas (combined) occurred in chemically exposed mice. Although lung lesions are relatively common in mice, the dose-related increases observed in the current studies are indicative of a chemical-related effect. Benzofuran is not a volatile liquid and is soluble in corn oil, and thus it is unlikely that inhalation of benzofuran vapor during gavage administration could account for the presence of alveolar/bronchiolar neoplasms.

Oral administration of other compounds containing the furan ring is known to cause pulmonary toxicity. The most thoroughly studied of these is 4-ipomeanol, which was identified as the lung edema factor responsible for the fatal lung disease that has occurred in cattle and other livestock fed mold-damaged sweet potatoes (Boyd, 1980). The mechanism responsible for the acute lung toxicity of 4-ipomeanol involves cytochrome P450 activation of the furan ring to a highly reactive intermediate. In the lung, cytochrome P450-containing nonciliated bronchiolar epithelial (clara) cells have been implicated as the primary target for toxicity associated with exposure to furan compounds (Boyd, 1980; Wolf et al., 1982).

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

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of benzofuran for male F344/N rats receiving doses of 30 or 60 mg/kg per day. There was *some evidence of carcinogenic activity* of benzofuran for female F344/N rats, based on increased incidences of tubular cell adenocarcinomas of the kidney. There was *clear evidence of carcinogenic activity* for male and female $B6C3F_1$ mice, based on increased incidences of neoplasms of the liver, lung, and forestomach.

Exposure to benzofuran increased the severity of nephropathy in male rats, increased the incidences of nephropathy in female rats, and induced hepatocellular metaplasia in the pancreas in female rats. Nonneoplastic lesions observed in mice exposed to benzofuran included syncytial alteration of the liver, bronchiolar epithelial hyperplasia, and epithelial hyperplasia of the forestomach.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Basal cell tumor	1 (2%)		1 (2%)
Keratoacanthoma	2 (4%)	1 (2%)	2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		1 (2%)
Fibroma	4 (8%)	1 (2%)	4 (8%)
Fibrosarcoma		2 (4%)	
Granular cell tumor, NOS			1 (2%)
Neurilemoma, malignant	14 (28%)	8 (16%)	6 (12%)
RESPIRATORY SYSTEM			
#Nose	(50)	(49)	(49)
Papillary adenoma			1 (2%)
#Lung	(50)	(50)	(48)
Squamous cell carcinoma			1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma		3 (6%)	2 (4%)
Fibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS		1 (2%)	
Leukemia, mononuclear cell	9 (18%)	13 (26%)	17 (34%)
#Lymph node	(50)	(49)	(47)
Squamous cell carcinoma, metastatic			1 (2%)
#Mesenteric lymph node	(50)	(49)	(47)
Carcinoma, NOS, metastatic		1 (2%)	
Fibrosarcoma, metastatic		1 (2%)	
#Liver	(50)	(50)	(49)
Leukemia, mononuclear cell	1 (2%)		
CIRCULATORY SYSTEM			
#Heart	(50)	(49)	(48)
Neurilemoma, malignant	3 (6%)	3 (6%)	4 (8%)
#Kidney	(50)	(50)	(49)
Hemangiosarcoma		1 (2%)	
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	
Squamous cell carcinoma		1 (2%)	
#Salivary gland	(46)	(39)	(41)
Carcinoma, NOS	1 (2%)		
Neurilemoma, malignant	1 (2%)	2 (5%)	2 (5%)
Neurilemoma, metastatic	1 (2%)	2 (5%)	
#Liver	(50)	(50)	(49)
Hepatocellular adenoma		1 (2%)	
Hepatocellular carcinoma	1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
Fibrosarcoma, metastatic		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(50)	(48)	(48)
Adenoma, NOS		1 (2%)	2 (4%)
Acinar cell adenoma	1 (2%)	1 (2%)	
#Esophagus	(50)	(47)	(45)
Squamous cell papilloma			1 (2%)
Neurilemoma, metastatic	1 (2%)		
#Stomach	(50)	(50)	(49)
Fibrosarcoma		1 (2%)	
Neurilemoma, malignant			1 (2%)
Neurilemoma, metastatic			1 (2%)
#Forestomach	(50)	(50)	(49)
Squamous cell papilloma	1 (2%)		1 (2%)
#Duodenum	(50)	(50)	(49)
Fibrosarcoma, metastatic		1 (2%)	
#Colon	(50)	(49)	(49)
Adenocarcinoma, NOS			1 (2%)
Adenomatous polyp, NOS		1 (2%)	
Sarcoma, NOS			1 (2%)
Leiomyoma			1 (2%)
#Cecum	(50)	(49)	(49)
Adenocarcinoma, NOS			1 (2%)
Lipoma		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Tubular cell adenoma	1 (2%)	1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary	(48)	(48)	(45)
Adenoma, NOS	18 (38%)	16 (33%)	22 (49%)
#Adrenal	(50)	(50)	(47)
Cortical adenoma			2 (4%)
#Adrenal medulla	(50)	(50)	(47)
Pheochromocytoma	14 (28%)	6 (12%)	10 (21%)
Ganglioneuroma	1 (2%)		
#Thyroid	(50)	(48)	(45)
Follicular cell carcinoma			3 (7%)
C-cell adenoma	5 (10%)	3 (6%)	3 (7%)
C-cell carcinoma	1 (2%)		
#Thyroid follicle	(50)	(48)	(45)
Papillary adenoma	2 (4%)	1 (2%)	
#Parathyroid	(40)	(38)	(36)
Adenoma, NOS	1 (3%)		
#Pancreatic islets	(50)	(48)	(48)
Islet cell adenoma	2 (4%)	2 (4%)	3 (6%)
Islet cell carcinoma	2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma			3 (6%)
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	
Adenoma, NOS	1 (2%)	1 (2%)	2 (4%)
#Testis	(50)	(48)	(47)
Interstitial cell tumor	42 (84%)	40 (83%)	41 (87%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Brain	(50)	(50)	(48)
Ependymoma		1 (2%)	
#Cerebellum	(50)	(50)	(48)
Astrocytoma		1 (2%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Paraganglioma, NOS			1 (2%)
Mesothelioma, NOS		1 (2%)	
Neurilemoma, malignant			1 (2%)
Neurilemoma, metastatic			1 (2%)
*Mesentery	(50)	(50)	(50)
Neurilemoma, metastatic	1 (2%)		
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	2 (4%)	1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
Neurilemoma, metastatic	1 (2%)		1 (2%)
Diaphragm			
Squamous cell carcinoma, metastatic			1
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	13	11
Moribund sacrifice	15	25	20
Terminal sacrifice	33	12	18
Dosing accident			1
TUMOR SUMMARY			
Total animals with primary tumors**	50	48	47
Total primary tumors	137	119	143
Total animals with benign tumors	49	48	46
Total benign tumors	98	78	99
Total animals with malignant tumors	31	33	31
Total malignant tumors	36	39	41
Total animals with secondary tumors##	3	5	5
Total secondary tumors	4	7	6
Total animals with tumors-- uncertain benign or malignant	3	2	3
Total uncertain tumors	3	2	3

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: VEHICLE CONTROL

ANIMAL NUMBER	0017	0003	0001	0002	0019	0050	0027	0030	0018	0005	0048	0010	0006	0029	0033	0046	0022	0004	0007	0008	0009	0011	0012	0013	0014
WEEKS ON STUDY	077	082	087	089	091	091	093	093	094	096	097	098	099	099	100	100	103	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor																									
Keratoacanthoma																					X				
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																X									
Fibroma							X																		
Neurilemoma, malignant		X		X		X	X		X			X		X	X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	+	−	+	+	−	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant													X												
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma				X																					
Salivary gland	−	−	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																							X		
Neurilemoma, malignant																									
Neurilemoma, metastatic																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Leukemia, mononuclear cell														X											
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																							X		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, metastatic																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma			X																						
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma					X																				
Urinary bladder	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X		X		X				X			X			X	X	X		X			X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma					X										X	X				X				X	
Ganglioneuroma																		X							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																									
C-cell adenoma									X						X							X			
C-cell carcinoma																								X	
Parathyroid	−	+	−	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	−	+	+	+
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma											X														

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0015	0016	0020	0021	0023	0024	0025	0026	0028	0031	0032	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0047	0049	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor				X																						1
Keratoacanthoma																						X				2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma				X		X						X														4
Neurilemoma, malignant						X	X	X		X		X									X					14
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	+	+	+	−	+	−	−	+	+	+	+	+	−	−	−	+	−	+	+	−	−	−	−	+	28
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, malignant				X							X															3
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, NOS																										1
Neurilemoma, malignant			X																							1
Neurilemoma, metastatic												X														1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																	X									1
Leukemia, mononuclear cell																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, metastatic												X														1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS					X			X		X			X		X					X	X			X			18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X				X		X		X						X		X	X			X		X			14
Ganglioneuroma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papillary adenoma									X						X											2
C cell adenoma				X								X														5
C cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	−	+	+	−	+	40
Adenoma, NOS						X																				1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma															X				X							2
Islet cell carcinoma								X																		2

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0017	0003	0001	0002	0019	0050	0027	0030	0018	0005	0048	0010	0006	0029	0033	0046	0022	0004	0007	0008	0009	0011	0012	0013	0014
WEEKS ON STUDY	077	082	087	089	091	091	093	093	094	096	097	098	099	099	100	100	103	104	104	104	104	104	104	104	104
REPRODUCTIVE SYSTEM																									
Mammary gland	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
Prostate	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																					X				
Adenoma, NOS								X																	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal 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																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS										X															
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma, metastatic														X											
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Neurilemoma, metastatic													X												
Leukemia, mononuclear cell					X		X		X	X							X								

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0 1 5	0 1 6	0 2 0	0 2 1	0 2 3	0 2 4	0 2 5	0 2 6	0 2 8	0 3 1	0 3 2	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 7	0 4 9	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	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	42
Prostate	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	44
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal 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																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																X										2
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma, 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	N	*50
Mesothelioma, NOS																								X		1
Neurilemoma, metastatic																										1
Leukemia, mononuclear cell	X				X				X						X											9

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: LOW DOSE

ANIMAL NUMBER	030	028	034	015	006	008	023	003	022	029	032	016	049	007	027	033	009	025	026	036	043	001	018	031	042
WEEKS ON STUDY	046	075	080	082	083	086	086	087	087	087	088	090	090	091	091	091	092	092	092	093	093	094	094	094	094
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Keratoacanthoma						X																			
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Fibroma										X															
Fibrosarcoma							X													X					
Neurilemoma, malignant						X									X	X			X			X	X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma													X												
Fibrosarcoma, metastatic							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																				X					
Fibrosarcoma, metastatic																									
Thymus	+	+	+	−	−	+	−	+	−	+	−	+	−	−	−	+	+	−	+	+	−	+	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																						X			
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																						X			
Squamous cell carcinoma																									
Salivary gland	+	+	+	−	−	−	−	+	−	+	−	+	−	+	+	+	+	+	−	+	+	+	+	+	+
Neurilemoma, malignant												X													
Neurilemoma, metastatic															X							X			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Fibrosarcoma, metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Acinar cell adenoma					X																				
Esophagus	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																X									
Lipoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Hemangiosarcoma																									
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X		X			X		X			X							X		X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma										X															
Thyroid	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma														X											
C cell adenoma																									
Parathyroid	+	+	−	+	−	+	−	+	+	+	−	−	−	+	−	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma															X										
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	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
Prostate	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																				X					
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ependymoma														X											
Astrocytoma			X																						
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																		X							
Tunica vaginalis	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS				X																					
Leukemia, mononuclear cell			X						X		X														

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

ANIMAL NUMBER	012	038	045	035	002	021	047	039	017	048	024	041	040	004	005	010	011	013	014	019	020	037	044	046	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	095	096	096	097	098	098	098	099	101	101	102	102	103	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Fibrosarcoma																										2
Neurilemoma, malignant						X	X																			8
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma		X																				X				3
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, metastatic																										1
Fibrosarcoma, metastatic																X										1
Thymus	+	–	–	–	–	+	–	–	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	28
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neurilemoma, malignant			X																X							3
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Squamous cell carcinoma				X																						1
Salivary gland	+	+	+	+	+	–	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	39
Neurilemoma, malignant								X																		2
Neurilemoma, metastatic																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma													X													1
Fibrosarcoma, metastatic																X										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS		X																								1
Acinar cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																X										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic																X										1
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenomatous polyp, NOS																										1
Lipoma															X											1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma		X																								1
Hemangiosarcoma																							X			1
Urinary bladder	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X		X		X			X					X		X			X	X				X			16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma				X					X		X										X			X		6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papillary adenoma																										1
C-cell adenoma		X											X											X		3
Parathyroid	–	+	+	+	–	–	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																								X		2
Islet cell carcinoma													X													1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	N	N	N	+	+	N	N	+	N	+	N	N	N	+	N	N	+	N	N	*50
Testis	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	40
Prostate	+	+	+	–	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
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												1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ependymoma																										1
Astrocytoma																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
Tunica vaginalis	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS		X																								1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										1
Leukemia, mononuclear cell	X		X	X					X			X		X	X	X	X								X	13

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: HIGH DOSE

ANIMAL NUMBER	0032	0014	0020	0117	0229	0330	0115	0227	0002	0111	0103	0250	0116	0335	0336	0118	0004	0223	0244	0001	0440	0444	0113	0009	0048
WEEKS ON STUDY	0533	0588	0700	0733	0755	0766	0777	0777	0822	0833	0877	0877	0899	0900	0900	0922	0933	0933	0933	0934	0944	0944	0955	0977	0977
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Basal cell tumor												X													
Keratoacanthoma											X														
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma			X			X																			
Granular cell tumor, NOS													X												
Neurilemoma, malignant									X				X									X		X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	−	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Alveolar/bronchiolar carcinoma																									
Trachea	−	+	+	+	+	+	+	+	+	−	+	+	+	+	C	+	+	+	+	+	−	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	−	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	−
Squamous cell carcinoma, metastatic							X																		
Thymus	−	−	+	+	+	+	+	+	−	−	+	+	+	+	C	−	+	−	+	+	−	−	−	−	+
CIRCULATORY SYSTEM																									
Heart	−	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																				X					
DIGESTIVE SYSTEM																									
Salivary gland	−	+	+	+	+	+	−	+	−	−	+	+	+	+	C	+	+	−	+	+	−	+	+	+	+
Neurilemoma, malignant																							X		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	−	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Esophagus	−	+	+	+	−	+	+	+	+	−	+	+	+	+	C	+	+	+	+	+	−	+	+	+	+
Squamous cell papilloma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Neurilemoma, malignant																									X
Neurilemoma, metastatic																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Sarcoma, NOS																									
Leiomyoma																									X
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	−	−	+	+	+	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	+	−	C	+	+	+	+	+	+	+	+	+	−
Adenoma, NOS										X			X			X		X		X		X	X	X	
Adrenal	+	−	−	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma									X								X	X					X		
Thyroid	−	+	+	+	+	+	+	+	+	−	+	+	+	+	C	+	+	+	+	+	−	+	+	+	+
Follicular cell carcinoma					X									X											
C-cell adenoma																									
Parathyroid	−	−	−	+	−	+	−	+	−	−	+	+	+	−	C	+	+	+	+	+	−	−	+	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	−	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma								X	X										X						
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	+	+	+	+	+	N	+	N	+	N	+	N	N	+	+	+	+	N	+	+	N	+
Fibroadenoma																	X								
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	−
Interstitial cell tumor					X	X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	+
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																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	+	+	+	+	−
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
Paraganglioma, NOS																									
Neurilemoma, malignant																		X							
Neurilemoma, metastatic																									X
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma, metastatic																									
Leukemia, mononuclear cell				X	X			X	X	X	X					X	X								
Diaphragm, NOS																									
Squamous cell carcinoma, metastatic							X																		

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

ANIMAL NUMBER	0049	0006	0022	0034	0019	0043	0047	0005	0007	0008	0010	0012	0021	0025	0026	0028	0031	0033	0037	0038	0039	0041	0042	0045	0046	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	098	099	099	100	101	101	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Basal cell tumor																										1
Keratoacanthoma															X											2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Sarcoma, NOS	X																									1
Fibroma				X																					X	4
Granular cell tumor, NOS																										1
Neurilemoma, malignant										X											X					6
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma																										1
Alveolar/bronchiolar carcinoma											X												X			2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary adenoma							X																			1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic																										1
Thymus	+	−	+	−	+	+	−	+	+	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+	−	32
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neurilemoma, malignant	X										X								X							4
DIGESTIVE SYSTEM																										
Salivary gland	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	41
Neurilemoma, malignant															X											2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, meta																							X			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																X										2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Squamous cell papilloma				X																						1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma											X															1
Neurilemoma, malignant																										1
Neurilemoma, metastatic										X																1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS										@X																1
Sarcoma, NOS																								X		1
Leiomyoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS					X	X		X		X		X		X	X			X		X	X	X	X	X	X	22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cortical adenoma	X									X																2
Pheochromocytoma							X				X		X								X	X			X	10
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Follicular cell carcinoma																				X						3
C-cell adenoma				X					X						X											3
Parathyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																										3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	N	*50
Fibroadenoma									X	X																3
Testis	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																				X						2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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
Paraganglioma, NOS								X																		1
Neurilemoma, malignant																										1
Neurilemoma, metastatic																										1
Tunica vaginalis	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS					X																					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma, metastatic											X															1
Leukemia, mononuclear cell	X	X	X		X					X						X				X				X	X	17
Diaphragm, NOS																										
Squamous cell carcinoma, metastatic																										1

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle Control	30 mg/kg	60 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	11.2%	2.3%	13.7%
Terminal Rates (c)	3/33 (9%)	0/12 (0%)	1/18 (6%)
Week of First Observation	93	87	70
Life Table Tests (d)	P=0.369	P=0.428N	P=0.410
Incidental Tumor Tests (d)	P=0.453N	P=0.236N	P=0.541N
Cochran-Armitage Trend Test (d)	P=0.583		
Fisher Exact Test (d)		P=0.181N	P=0.643
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	11.2%	7.6%	13.7%
Terminal Rates (c)	3/33 (9%)	0/12 (0%)	1/18 (6%)
Week of First Observation	93	86	70
Life Table Tests (d)	P=0.360	P=0.527	P=0.410
Incidental Tumor Tests (d)	P=0.424N	P=0.461N	P=0.541N
Cochran-Armitage Trend Test (d)	P=0.576		
Fisher Exact Test (d)		P=0.500N	P=0.643
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	13.6%	7.6%	17.1%
Terminal Rates (c)	3/33 (9%)	0/12 (0%)	1/18 (6%)
Week of First Observation	93	86	70
Life Table Tests (d)	P=0.328	P=0.620	P=0.361
Incidental Tumor Tests (d)	P=0.397N	P=0.274N	P=0.483N
Cochran-Armitage Trend Test (d)	P=0.571		
Fisher Exact Test (d)		P=0.357N	P=0.630
Subcutaneous Tissue: Malignant Neurilemoma			
Overall Rates (a)	14/50 (28%)	8/50 (16%)	6/50 (12%)
Adjusted Rates (b)	32.5%	24.4%	21.3%
Terminal Rates (c)	6/33 (18%)	0/12 (0%)	2/18 (11%)
Week of First Observation	82	86	82
Life Table Tests (d)	P=0.218N	P=0.567N	P=0.251N
Incidental Tumor Tests (d)	P=0.017N	P=0.012N	P=0.032N
Cochran-Armitage Trend Test (d)	P=0.027N		
Fisher Exact Test (d)		P=0.114N	P=0.040N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (e)	0/50 (0%)	3/50 (6%)	2/48 (4%)
Adjusted Rates (b)	0.0%	14.4%	11.1%
Terminal Rates (c)	0/33 (0%)	1/12 (8%)	2/18 (11%)
Week of First Observation		90	104
Life Table Tests (d)	P=0.098	P=0.044	P=0.118
Incidental Tumor Tests (d)	P=0.126	P=0.143	P=0.118
Cochran-Armitage Trend Test (d)	P=0.190		
Fisher Exact Test (d)		P=0.121	P=0.237
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (e)	1/50 (2%)	3/50 (6%)	2/48 (4%)
Adjusted Rates (b)	2.2%	14.4%	11.1%
Terminal Rates (c)	0/33 (0%)	1/12 (8%)	2/18 (11%)
Week of First Observation	91	90	104
Life Table Tests (d)	P=0.227	P=0.159	P=0.332
Incidental Tumor Tests (d)	P=0.304	P=0.475	P=0.400
Cochran-Armitage Trend Test (d)	P=0.383		
Fisher Exact Test (d)		P=0.309	P=0.485

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	30 mg/kg	60 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	10/50 (20%)	13/50 (26%)	17/50 (34%)
Adjusted Rates (b)	24.4%	58.0%	50.4%
Terminal Rates (c)	4/33 (12%)	5/12 (42%)	5/18 (28%)
Week of First Observation	91	80	73
Life Table Tests (d)	P=0.006	P=0.015	P=0.011
Incidental Tumor Tests (d)	P=0.104	P=0.362	P=0.213
Cochran-Armitage Trend Test (d)	P=0.071		
Fisher Exact Test (d)		P=0.317	P=0.088
Heart: Malignant Neurilemoma			
Overall Rates (e)	3/50 (6%)	3/49 (6%)	4/48 (8%)
Adjusted Rates (b)	8.5%	15.2%	17.4%
Terminal Rates (c)	2/33 (6%)	1/12 (8%)	2/18 (11%)
Week of First Observation	99	94	94
Life Table Tests (d)	P=0.184	P=0.296	P=0.240
Incidental Tumor Tests (d)	P=0.322	P=0.572	P=0.401
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.651	P=0.477
Pituitary Gland: Adenoma			
Overall Rates (e)	18/48 (38%)	16/48 (33%)	22/45 (49%)
Adjusted Rates (b)	47.1%	57.9%	79.2%
Terminal Rates (c)	12/31 (39%)	4/12 (33%)	12/17 (71%)
Week of First Observation	87	83	83
Life Table Tests (d)	P=0.008	P=0.060	P=0.007
Incidental Tumor Tests (d)	P=0.037	P=0.466N	P=0.042
Cochran-Armitage Trend Test (d)	P=0.160		
Fisher Exact Test (d)		P=0.416N	P=0.184
Adrenal Medulla: Pheochromocytoma			
Overall Rates (e)	14/50 (28%)	6/50 (12%)	10/47 (21%)
Adjusted Rates (b)	38.4%	31.7%	39.4%
Terminal Rates (c)	11/33 (33%)	2/12 (17%)	5/18 (28%)
Week of First Observation	91	87	82
Life Table Tests (d)	P=0.367	P=0.602N	P=0.395
Incidental Tumor Tests (d)	P=0.459N	P=0.173N	P=0.526N
Cochran-Armitage Trend Test (d)	P=0.233N		
Fisher Exact Test (d)		P=0.040N	P=0.298N
Thyroid Gland: Follicular Cell Carcinoma			
Overall Rates (e)	0/50 (0%)	0/48 (0%)	3/45 (7%)
Adjusted Rates (b)	0.0%	0.0%	10.2%
Terminal Rates (c)	0/33 (0%)	0/12 (0%)	1/18 (6%)
Week of First Observation			75
Life Table Tests (d)	P=0.024	(f)	P=0.074
Incidental Tumor Tests (d)	P=0.055	(f)	P=0.171
Cochran-Armitage Trend Test (d)	P=0.031		
Fisher Exact Test (d)		(f)	P=0.103
Thyroid Gland: Papillary Adenoma or Follicular Cell Carcinoma			
Overall Rates (e)	2/50 (4%)	1/48 (2%)	3/45 (7%)
Adjusted Rates (b)	6.1%	2.7%	10.2%
Terminal Rates (c)	2/33 (6%)	0/12 (0%)	1/18 (6%)
Week of First Observation	104	91	75
Life Table Tests (d)	P=0.244	P=0.727	P=0.313
Incidental Tumor Tests (d)	P=0.400	P=0.613N	P=0.492
Cochran-Armitage Trend Test (d)	P=0.358		
Fisher Exact Test (d)		P=0.515N	P=0.450

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	30 mg/kg	60 mg/kg
Thyroid Gland: C-Cell Adenoma			
Overall Rates (e)	5/50 (10%)	3/48 (6%)	3/45 (7%)
Adjusted Rates (b)	13.7%	18.9%	15.2%
Terminal Rates (c)	3/33 (9%)	1/12 (8%)	2/18 (11%)
Week of First Observation	94	96	100
Life Table Tests (d)	P=0.529	P=0.482	P=0.630
Incidental Tumor Tests (d)	P=0.437N	P=0.468N	P=0.517N
Cochran-Armitage Trend Test (d)	P=0.334N		
Fisher Exact Test (d)		P=0.381N	P=0.418N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (e)	6/50 (12%)	3/48 (6%)	3/45 (7%)
Adjusted Rates (b)	16.6%	18.9%	15.2%
Terminal Rates (c)	4/33 (12%)	1/12 (8%)	2/18 (11%)
Week of First Observation	94	96	100
Life Table Tests (d)	P=0.505N	P=0.562	P=0.559N
Incidental Tumor Tests (d)	P=0.332N	P=0.390N	P=0.415N
Cochran-Armitage Trend Test (d)	P=0.220N		
Fisher Exact Test (d)		P=0.264N	P=0.299N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (e)	2/50 (4%)	2/48 (4%)	3/48 (6%)
Adjusted Rates (b)	6.1%	10.8%	7.4%
Terminal Rates (c)	2/33 (6%)	1/12 (8%)	0/18 (0%)
Week of First Observation	104	91	77
Life Table Tests (d)	P=0.250	P=0.389	P=0.347
Incidental Tumor Tests (d)	P=0.435	P=0.523	P=0.590
Cochran-Armitage Trend Test (d)	P=0.389		
Fisher Exact Test (d)		P=0.676	P=0.480
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (e)	4/50 (8%)	3/48 (6%)	3/48 (6%)
Adjusted Rates (b)	11.4%	17.7%	7.4%
Terminal Rates (c)	3/33 (9%)	1/12 (8%)	0/18 (0%)
Week of First Observation	97	91	77
Life Table Tests (d)	P=0.484	P=0.382	P=0.601
Incidental Tumor Tests (d)	P=0.393N	P=0.639N	P=0.441N
Cochran-Armitage Trend Test (d)	P=0.442N		
Fisher Exact Test (d)		P=0.523N	P=0.523N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	13.7%
Terminal Rates (c)	0/33 (0%)	0/12 (0%)	2/18 (11%)
Week of First Observation			93
Life Table Tests (d)	P=0.019	(f)	P=0.051
Incidental Tumor Tests (d)	P=0.023	(f)	P=0.074
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		(f)	P=0.121
Testis: Interstitial Cell Tumor			
Overall Rates (e)	42/50 (84%)	40/48 (83%)	41/47 (87%)
Adjusted Rates (b)	95.4%	100.0%	100.0%
Terminal Rates (c)	31/33 (94%)	12/12 (100%)	18/18 (100%)
Week of First Observation	77	80	75
Life Table Tests (d)	P=0.001	P<0.001	P=0.001
Incidental Tumor Tests (d)	P=0.038	P=0.100	P=0.064
Cochran-Armitage Trend Test (d)	P=0.384		
Fisher Exact Test (d)		P=0.572N	P=0.436

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	30 mg/kg	60 mg/kg
All Sites: Mesothelioma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	8.4%	7.0%	4.8%
Terminal Rates (c)	2/33 (6%)	0/12 (0%)	0/18 (0%)
Week of First Observation	96	92	101
Life Table Tests (d)	P=0.413N	P=0.579	P=0.506N
Incidental Tumor Tests (d)	P=0.221N	P=0.471N	P=0.341N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
All Sites: Benign Tumors			
Overall Rates (a)	49/50 (98%)	48/50 (96%)	46/50 (92%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	33/33 (100%)	12/12 (100%)	18/18 (100%)
Week of First Observation	77	80	70
Life Table Tests (d)	P=0.003	P<0.001	P=0.003
Incidental Tumor Tests (d)	P=0.641	P=0.636	P=0.688N
Cochran-Armitage Trend Test (d)	P=0.118N		
Fisher Exact Test (d)		P=0.500N	P=0.182N
All Sites: Malignant Tumors			
Overall Rates (a)	31/50 (62%)	33/50 (66%)	31/50 (62%)
Adjusted Rates (b)	65.9%	87.1%	77.1%
Terminal Rates (c)	17/33 (52%)	8/12 (67%)	10/18 (56%)
Week of First Observation	82	80	73
Life Table Tests (d)	P=0.022	P=0.001	P=0.033
Incidental Tumor Tests (d)	P=0.512N	P=0.481N	P=0.467N
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.417	P=0.581
All Sites: All Tumors			
Overall Rates (a)	50/50 (100%)	48/50 (96%)	47/50 (94%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	33/33 (100%)	12/12 (100%)	18/18 (100%)
Week of First Observation	77	80	70
Life Table Tests (d)	P=0.003	P<0.001	P=0.003
Incidental Tumor Tests (d)	P=0.399N	P=0.500N	P=0.434N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.248N	P=0.122N

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined microscopically at the site
(f) No P value is reported because no tumors were observed in the 30 mg/kg and vehicle control groups.

TABLE A4a. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Neurilemomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	1/50
Ampicillin trihydrate	0/50
Penicillin VK	4/50
TOTAL	5/150 (3.3%)
SD (b)	4.16%
Range (c)	
High	4/50
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 8/2,099 (0.4%)
SD (b)	1.41%
Range (c)	
High	4/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one malignant neurilemoma

TABLE A4b. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Leukemia in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	13/50
Ampicillin trihydrate	5/50
Penicillin VK	14/50
TOTAL	32/150 (21.3%)
SD (b)	9.87%
Range (c)	
High	14/50
Low	5/50
Overall Historical Incidence	
TOTAL	361/2,099 (17.2%)
SD (b)	9.04%
Range (c)	
High	22/50
Low	1/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4c. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
N,N-Dimethylaniline	11/47	0/47	11/47
Ampicillin trihydrate	11/46	1/46	12/46
Penicillin VK	10/48	0/48	10/48
TOTAL	32/141 (22.7%)	1/141 (0.7%)	33/141 (23.4%)
SD (b)	1.65%	1.26%	2.63%
Range (c)			
High	11/46	1/46	12/46
Low	10/48	0/48	10/48
Overall Historical Incidence			
TOTAL	(d) 563/2,044 (27.5%)	(e) 39/2,044 (1.9%)	(d,e) 601/2,044 (29.4%)
SD (b)	10.60%	2.55%	10.68%
Range (c)			
High	26/48	4/47	26/48
Low	5/50	0/50	6/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes 43 chromophobe adenomas and 1 acidophil adenoma
(e) Includes three adenocarcinomas, NOS, and five chromophobe carcinomas

TABLE A4d. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	0/49
Ampicillin trihydrate	0/44
Penicillin VK	0/45
TOTAL	0/138
SD (b)	0.00%
Range (c)	
High	0/49
Low	0/49
Overall Historical Incidence	
TOTAL	(d) 7/2,072 (0.3%)
SD (b)	0.76%
Range (c)	
High	1/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one papilloma, NOS, five squamous cell papillomas, and one squamous cell carcinoma

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	49
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
RESPIRATORY SYSTEM			
#Nose	(50)	(49)	(49)
Hemorrhage		1 (2%)	1 (2%)
Inflammation, acute	4 (8%)	6 (12%)	4 (8%)
Inflammation, acute/chronic	3 (6%)	1 (2%)	3 (6%)
Inflammation, chronic	2 (4%)	1 (2%)	
Degeneration, hyaline	42 (84%)	21 (43%)	33 (67%)
Hyperplasia, papillary		2 (4%)	1 (2%)
#Bronchial mucosa	(50)	(50)	(48)
Hyperplasia, nodular		1 (2%)	
#Bronchial submucosa	(50)	(50)	(48)
Hemosiderosis		1 (2%)	
#Lung	(50)	(50)	(48)
Foreign body, NOS			1 (2%)
Congestion, NOS		1 (2%)	1 (2%)
Hemorrhage		1 (2%)	3 (6%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, interstitial	6 (12%)	6 (12%)	10 (21%)
Bronchopneumonia, acute			1 (2%)
Perivascular cuffing	14 (28%)		13 (27%)
Foreign material, NOS			1 (2%)
Alveolar macrophages	3 (6%)	6 (12%)	3 (6%)
Hyperplasia, adenomatous	5 (10%)	2 (4%)	5 (10%)
HEMATOPOIETIC SYSTEM			
*Blood	(50)	(50)	(50)
Leukocytosis, NOS	3 (6%)		4 (8%)
Leukocytosis, neutrophilic		2 (4%)	
#Bone marrow	(50)	(49)	(48)
Fibrosis	2 (4%)	3 (6%)	2 (4%)
Hyperplasia, erythroid			2 (4%)
Hyperplasia, granulocytic	1 (2%)	1 (2%)	1 (2%)
#Spleen	(50)	(50)	(49)
Hemorrhage	1 (2%)		
Fibrosis	1 (2%)		2 (4%)
Infarct, focal		1 (2%)	
Hemosiderosis	44 (88%)	46 (92%)	46 (94%)
Atrophy, NOS			1 (2%)
Atrophy, diffuse		1 (2%)	
Depletion, lymphoid		1 (2%)	
Hyperplasia, reticulum cell	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis	1 (2%)	2 (4%)	4 (8%)
Erythropoiesis		5 (10%)	1 (2%)
#Lymph node	(50)	(49)	(47)
Congestion, NOS			1 (2%)
Inflammation, acute/chronic			1 (2%)
#Submandibular lymph node	(50)	(49)	(47)
Hemorrhage	1 (2%)		
Hyperplasia, lymphoid	2 (4%)	3 (6%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mediastinal lymph node	(50)	(49)	(47)
Hemorrhage		1 (2%)	1 (2%)
Hemosiderosis		2 (4%)	
Mastocytosis			1 (2%)
#Mesenteric lymph node	(50)	(49)	(47)
Edema, NOS		1 (2%)	
Hemorrhage	1 (2%)	1 (2%)	
#Glandular stomach	(50)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
#Duodenum	(50)	(50)	(49)
Hyperplasia, lymphoid			1 (2%)
#Thymus	(28)	(28)	(32)
Ultimobranchial cyst	2 (7%)	2 (7%)	
CIRCULATORY SYSTEM			
#Pancreatic lymph node	(50)	(49)	(47)
Lymphangiectasis			1 (2%)
#Mesenteric lymph node	(50)	(49)	(47)
Lymphangiectasis		1 (2%)	
#Heart	(50)	(49)	(48)
Myxomatosis, cardiac valve	1 (2%)		
Fibrosis			1 (2%)
Hypertrophy, NOS			1 (2%)
#Heart/atrium	(50)	(49)	(48)
Hypertrophy, diffuse		1 (2%)	
#Left atrium	(50)	(49)	(48)
Thrombus, mural			1 (2%)
Hypertrophy, NOS	1 (2%)		
#Myocardium	(50)	(49)	(48)
Inflammation, chronic	14 (28%)	6 (12%)	10 (21%)
Fibrosis	31 (62%)	29 (59%)	21 (44%)
#Endocardium	(50)	(49)	(48)
Fibrosis			1 (2%)
#Cardiac valve	(50)	(49)	(48)
Endocardiosis		1 (2%)	
*Pulmonary artery	(50)	(50)	(50)
Mineralization	10 (20%)	23 (46%)	3 (6%)
*Mesenteric artery	(50)	(50)	(50)
Periarteritis	1 (2%)	1 (2%)	
#Kidney	(50)	(50)	(49)
Periarteritis	2 (4%)		
#Testis	(50)	(48)	(47)
Periarteritis			1 (2%)
#Adrenal medulla	(50)	(50)	(47)
Thrombosis, NOS			1 (2%)
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Hyperplasia, epithelial		2 (4%)	1 (2%)
#Salivary gland	(46)	(39)	(41)
Lymphocytic inflammatory infiltrate	2 (4%)	1 (3%)	
Inflammation, acute diffuse		1 (3%)	
Inflammation, acute/chronic	1 (2%)		
Fibrosis, diffuse	1 (2%)		
Degeneration, NOS	3 (7%)		1 (2%)
Atrophy, NOS	3 (7%)	7 (18%)	5 (12%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver	(50)	(50)	(49)
Hernia, NOS	5 (10%)		1 (2%)
Congestion, NOS	2 (4%)		
Lymphocytic inflammatory infiltrate	1 (2%)		
Degeneration, NOS	5 (10%)	1 (2%)	4 (8%)
Degeneration, cystic	2 (4%)		
Necrosis, focal	1 (2%)	1 (2%)	1 (2%)
Necrosis, diffuse		2 (4%)	2 (4%)
Metamorphosis, fatty	3 (6%)	2 (4%)	
Focal cellular change	34 (68%)	8 (16%)	14 (29%)
Clear cell change			1 (2%)
Pleomorphism		1 (2%)	1 (2%)
Hyperplasia, nodular			2 (4%)
#Intrahepatic bile duct	(50)	(50)	(49)
Cyst, NOS	1 (2%)		
Multiple cysts			1 (2%)
Hyperplasia, NOS	35 (70%)	28 (56%)	34 (69%)
#Liver/centrilobular	(50)	(50)	(49)
Necrosis, NOS		1 (2%)	
Metamorphosis, fatty			1 (2%)
#Liver/periportal	(50)	(50)	(49)
Metamorphosis, fatty	4 (8%)	2 (4%)	3 (6%)
#Pancreas	(50)	(48)	(48)
Ectopia	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)		
Perivascular cuffing	1 (2%)		
Atrophy, focal	16 (32%)	6 (13%)	17 (35%)
Atrophy, diffuse		1 (2%)	
Hyperplasia, nodular	2 (4%)	4 (8%)	6 (13%)
#Esophagus	(50)	(47)	(45)
Hemorrhage		1 (2%)	
Ulcer, NOS			1 (2%)
Inflammation, chronic diffuse	1 (2%)		
#Glandular stomach	(50)	(50)	(49)
Mineralization		1 (2%)	
Cyst, NOS	1 (2%)		
Edema, NOS		4 (8%)	
Ulcer, NOS		1 (2%)	
Eosinophilic leukocytic infiltrate		1 (2%)	
Inflammation, chronic		1 (2%)	1 (2%)
Erosion		1 (2%)	1 (2%)
Hyperplasia, epithelial		1 (2%)	1 (2%)
#Forestomach	(50)	(50)	(49)
Cyst, NOS		1 (2%)	
Edema, NOS		3 (6%)	
Ulcer, NOS	1 (2%)	5 (10%)	8 (16%)
Inflammation, acute/chronic	3 (6%)		
Inflammation, chronic	1 (2%)	11 (22%)	6 (12%)
Erosion	1 (2%)	1 (2%)	
Hyperplasia, epithelial	9 (18%)	15 (30%)	18 (37%)
#Pylorus	(50)	(50)	(49)
Hyperplasia, adenomatous			1 (2%)
#Duodenum	(50)	(50)	(49)
Inflammation, acute			1 (2%)
#Colon	(50)	(49)	(49)
Parasitism	11 (22%)	6 (12%)	3 (6%)
#Cecum	(50)	(49)	(49)
Edema, NOS		1 (2%)	
Inflammation, acute diffuse		1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Hydronephrosis	2 (4%)	2 (4%)	
Cyst, NOS	1 (2%)		
Inflammation, acute		1 (2%)	1 (2%)
Nephropathy	49 (98%)	49 (98%)	48 (98%)
Infarct, focal			1 (2%)
Hyperplasia, atypical			1 (2%)
#Kidney/cortex	(50)	(50)	(49)
Cyst, NOS		16 (32%)	6 (12%)
#Kidney/tubule	(50)	(50)	(49)
Degeneration, hyaline		1 (2%)	
Metamorphosis, fatty		1 (2%)	
Pigmentation, NOS	2 (4%)	2 (4%)	2 (4%)
Hypertrophy, NOS		1 (2%)	
#Kidney/pelvis	(50)	(50)	(49)
Inflammation, acute	1 (2%)		
Hyperplasia, papillary	1 (2%)	22 (44%)	8 (16%)
#Urinary bladder	(48)	(45)	(46)
Lymphocytic inflammatory infiltrate	2 (4%)		
Inflammation, acute diffuse		1 (2%)	
Inflammation, chronic diffuse		1 (2%)	
#Urinary bladder/mucosa	(48)	(45)	(46)
Hyperplasia, diffuse	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(48)	(48)	(45)
Cyst, NOS	8 (17%)	5 (10%)	10 (22%)
Hemorrhagic cyst	1 (2%)		
Hemosiderosis	1 (2%)		
Hyperplasia, chromophobe cell	11 (23%)	8 (17%)	14 (31%)
Angiectasis	1 (2%)		
#Pituitary acidophil	(48)	(48)	(45)
Hyperplasia, NOS	1 (2%)		
#Adrenal cortex	(50)	(50)	(47)
Ectopia		1 (2%)	3 (6%)
Inflammation, acute diffuse		1 (2%)	
Degeneration, NOS		1 (2%)	
Metamorphosis, fatty	7 (14%)	6 (12%)	13 (28%)
Hyperplasia, nodular	14 (28%)	11 (22%)	10 (21%)
Hyperplasia, diffuse		1 (2%)	
#Adrenal medulla	(50)	(50)	(47)
Cyst, NOS			1 (2%)
Hyperplasia, focal	12 (24%)	10 (20%)	9 (19%)
#Thyroid	(50)	(48)	(45)
Ultimobranchial cyst	1 (2%)		1 (2%)
Cystic follicles	2 (4%)	4 (8%)	9 (20%)
Hyperplasia, C-cell	17 (34%)	6 (13%)	4 (9%)
Hyperplasia, follicular cell		1 (2%)	
#Thyroid follicle	(50)	(48)	(45)
Metaplasia, squamous			1 (2%)
#Parathyroid	(40)	(38)	(36)
Hyperplasia, NOS		8 (21%)	3 (8%)
#Pancreatic islets	(50)	(48)	(48)
Cytologic alteration, NOS			1 (2%)
Atrophy, NOS			1 (2%)
Hyperplasia, NOS	2 (4%)		
Metaplasia, NOS			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hemorrhage	2 (4%)		
Hyperplasia, cystic	9 (18%)	12 (24%)	11 (22%)
*Preputial gland	(50)	(50)	(50)
Inflammation, acute/chronic	10 (20%)	3 (6%)	5 (10%)
Inflammation, chronic	28 (56%)	34 (68%)	29 (58%)
Hyperplasia, nodular	1 (2%)	1 (2%)	
Hyperplasia, cystic	1 (2%)		
#Prostate	(44)	(45)	(49)
Inflammation, acute	6 (14%)	15 (33%)	10 (20%)
Inflammation, acute/chronic	9 (20%)	6 (13%)	8 (16%)
Inflammation, chronic	8 (18%)	1 (2%)	5 (10%)
Degeneration, cystic	8 (18%)	18 (40%)	6 (12%)
Degeneration, mucoid			1 (2%)
Atrophy, NOS			1 (2%)
Hyperplasia, focal		1 (2%)	
Hyperplasia, papillary		1 (2%)	
Hyperplasia, adenomatous		1 (2%)	
*Seminal vesicle	(50)	(50)	(50)
Atrophy, NOS	2 (4%)	1 (2%)	1 (2%)
*Coagulating gland	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
#Testis	(50)	(48)	(47)
Atrophy, NOS	7 (14%)	5 (10%)	3 (6%)
Hyperplasia, interstitial cell	9 (18%)	9 (19%)	10 (21%)
#Spermatogenic epithelial	(50)	(48)	(47)
Multinucleate giant cell		1 (2%)	
*Epididymis	(50)	(50)	(50)
Edema, NOS	1 (2%)	1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	1 (2%)		2 (4%)
Inflammation, granulomatous focal			1 (2%)
Fibrosis, focal		1 (2%)	
Degeneration, NOS		1 (2%)	
Cytoplasmic vacuolization	15 (30%)	14 (28%)	15 (30%)
Hyperplasia, NOS	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(48)
Inflammation, acute diffuse		1 (2%)	
#Brain	(50)	(50)	(48)
Hemorrhage			2 (4%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	1 (2%)
*Eye/anterior chamber	(50)	(50)	(50)
Hemorrhage	1 (2%)		
*Eye/retina	(50)	(50)	(50)
Hernia, NOS		1 (2%)	
Degeneration, NOS	18 (36%)	1 (2%)	1 (2%)
*Eye/lens, cortex	(50)	(50)	(50)
Cataract	16 (32%)	4 (8%)	1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic	2 (4%)		2 (4%)
Inflammation, chronic	22 (44%)	2 (4%)	12 (24%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy		4 (8%)	3 (6%)
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Edema, NOS	1 (2%)		
*Mediastinum	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Inflammation, chronic diffuse			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Edema, NOS	1 (2%)		
Inflammation, acute/chronic			2 (4%)
*Epicardium	(50)	(50)	(50)
Hemosiderosis	1 (2%)		
*Mesentery	(50)	(50)	(50)
Necrosis, fat	1 (2%)	3 (6%)	1 (2%)
*Tunica vaginalis	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
Perivascular cuffing			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
Necropsy performed/no histology performed			1

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

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)	1 (2%)	2 (4%)
Fibrosarcoma	1 (2%)		1 (2%)
Lipoma	1 (2%)		
Neurilemoma, malignant	1 (2%)	9 (18%)	3 (6%)
RESPIRATORY SYSTEM			
#Nasal gland	(49)	(14)	(49)
Adenocarcinoma, NOS			1 (2%)
#Lung	(50)	(50)	(49)
Alveolar/bronchiolar adenoma		1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma		1 (2%)	
C-cell carcinoma, metastatic	1 (2%)		
Pheochromocytoma, metastatic	1 (2%)		
Neurilemoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	19 (38%)	15 (30%)	18 (36%)
#Spleen	(50)	(50)	(49)
Neurilemoma, metastatic		1 (2%)	
#Thymus	(34)	(6)	(31)
Cystadenoma, NOS	1 (3%)		
Malignant lymphoma, histiocytic type			1 (3%)
CIRCULATORY SYSTEM			
#Heart	(49)	(50)	(49)
Neurilemoma, malignant	3 (6%)		
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
*Tongue	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	3 (6%)
#Liver	(50)	(50)	(49)
Hepatocellular adenoma			1 (2%)
Neurilemoma, metastatic		1 (2%)	
#Pancreas	(50)	(50)	(49)
Acinar cell carcinoma			1 (2%)
#Glandular stomach	(50)	(13)	(49)
Fibrosarcoma		1 (8%)	
#Forestomach	(50)	(13)	(49)
Squamous cell carcinoma			1 (2%)
*Rectum	(50)	(50)	(50)
Neurilemoma, metastatic		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenocarcinoma		1 (2%)	4 (8%)
Lipoma		1 (2%)	
#Urinary bladder	(46)	(8)	(44)
Neurilemoma, metastatic	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(49)	(50)	(48)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	19 (39%)	21 (42%)	12 (25%)
#Adrenal medulla	(50)	(9)	(49)
Pheochromocytoma		1 (11%)	
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(48)	(48)	(49)
Follicular cell adenoma		1 (2%)	
C-cell adenoma	8 (17%)	4 (8%)	5 (10%)
C-cell carcinoma	1 (2%)		
#Thyroid follicle	(48)	(48)	(49)
Papillary adenoma	1 (2%)		3 (6%)
#Pancreatic islets	(50)	(50)	(49)
Islet cell adenoma		1 (2%)	
Islet cell carcinoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
Fibroadenoma	16 (32%)	18 (36%)	17 (34%)
*Clitoral gland	(50)	(50)	(50)
Adenoma, NOS	3 (6%)		
Endometrial stromal sarcoma, metastatic	1 (2%)		
*Vagina	(50)	(50)	(50)
Endometrial stromal sarcoma	1 (2%)		
Neurilemoma, malignant	1 (2%)		
Neurilemoma, metastatic		1 (2%)	
#Uterus	(49)	(45)	(49)
Endometrial stromal polyp	7 (14%)	6 (13%)	3 (6%)
Neurilemoma, metastatic	1 (2%)		
Deciduoma		1 (2%)	
#Fallopian tube	(49)	(45)	(49)
Leiomyosarcoma			1 (2%)
#Ovary	(50)	(16)	(49)
Neurilemoma, malignant	2 (4%)		
NERVOUS SYSTEM			
#Brain	(50)	(9)	(49)
Granular cell tumor, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	1 (2%)
Adenoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Neoplasm, malignant, NOS			1 (2%)
ALL OTHER SYSTEMS			
Site unknown			
Squamous cell papilloma			1
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	5	7
Moribund sacrifice	17	22	14
Terminal sacrifice	27	23	25
Dosing accident			3
Accidentally killed, nda			1
TUMOR SUMMARY			
Total animals with primary tumors**	46	48	42
Total primary tumors	91	86	84
Total animals with benign tumors	37	41	30
Total benign tumors	59	58	50
Total animals with malignant tumors	27	24	28
Total malignant tumors	31	28	34
Total animals with secondary tumors##	5	2	
Total secondary tumors	5	5	
Total animals with tumors-- uncertain benign or malignant	1		
Total uncertain tumors	1		

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: VEHICLE CONTROL

ANIMAL NUMBER	0021	0004	0031	0035	0008	0049	0036	0012	0026	0038	0002	0006	0032	0041	0028	0025	0045	0010	0037	0044	0013	0019	0034	0001	0003
WEEKS ON STUDY	046	067	075	082	083	086	087	088	089	092	093	093	093	093	095	098	098	100	100	100	101	102	103	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma						X																			
Fibrosarcoma							X																		
Lipoma																		X							
Neurilemoma, malignant																						X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																		X							
Pheochromocytoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	–	–	+	+	+	–	+	+	+	+	+	–	–	–	+	–	+	+	+	+	–	+
Cystadenoma, NOS																									
CIRCULATORY SYSTEM																									
Heart	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																									
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	–	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, metastatic															X										
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS					X																				
Adenoma, NOS								X		X						X	X					X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, malignant																									
Thyroid	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																									
C-cell adenoma												X													
C-cell carcinoma																		X							
Parathyroid	–	–	–	–	+	+	+	+	–	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	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
Adenoma, NOS						X								X											
Endometrial stromal sarcoma, metastatic			X																						
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Endometrial stromal sarcoma			X																						
Neurilemoma, malignant															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Endometrial stromal polyp																	X					X			
Neurilemoma, metastatic																				X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant												X								X					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell								X	X		X		X				X		X		X	X	X		X

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0005	0007	0009	0011	0014	0015	0016	0017	0018	0020	0022	0023	0024	0027	0029	0030	0033	0039	0040	0042	0043	0046	0047	0048	0050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Fibrosarcoma																										1
Lipoma																										1
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic																										1
Pheochromocytoma, metastatic										X																1
Trachea	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	–	+	–	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	–	+	+	–	+	34
Cystadenoma, NOS																				X						1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neurilemoma, malignant					X			X													X					3
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma									X																	1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	46
Neurilemoma, metastatic																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Carcinoma, NOS																										1
Adenoma, NOS	X	X			X		X				X		X		X	X	X	X	X				X		X	19
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, malignant										X																1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
Papillary adenoma																							X			1
C-cell adenoma			X				X	X	X	X		X			X											8
C-cell carcinoma																										1
Parathyroid	–	+	+	–	–	+	+	+	+	–	+	+	+	–	+	+	–	+	+	+	+	–	–	+	+	33
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																									X	1
Fibroadenoma					X						X		X	X	X		X	X	X		X		X	X		16
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
Endometrial stromal sarcoma, metastatic																										1
Vagina	N	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
Endometrial stromal sarcoma																										1
Neurilemoma, malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp		X		X				X		X							X									7
Neurilemoma, metastatic																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, malignant																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS					X																					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell			X		X	X				X		X			X		X			X	X				19

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: LOW DOSE

ANIMAL NUMBER	0292	0293	0336	0442	0447	0088	0033	0339	0144	0441	0491	0491	0492	0935	0935	0935	0935	0936	0938	0999	0999	1001	1011	1011	1012
WEEKS ON STUDY	0556	0668	0775	0766	0777	0779	0880	0882	0888	0911	0911	0911	0912	0933	0933	0933	0935	0936	0938	0999	0999	1000	1011	1011	1012
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibroma																									
Neurilemoma, malignant											X	X	X			X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Neurilemoma, metastatic											X														
Trachea	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−
Nasal cavity	+	+	+	+	+	+	+	+	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, metastatic										X															
Lymph nodes	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Thymus	+	−	+	+	−	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	−	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, metastatic										X															
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	+	−	−	+	−	−	−	+	−
Fibrosarcoma			X																						
Small intestine	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Large intestine	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Rectum	+	+	+	+	+	+	N	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma, metastatic										X															
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Lipoma																									
Urinary bladder	−	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X				X	X		X	X				X			X	X			X	X		X		
Adrenal	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Pheochromocytoma							X																		
Thyroid	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma											X														
Parathyroid	+	−	+	+	−	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																					X				
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	+	+	N	N	N	+	+	+	+	+	+	N	+	N	+	+	N
Fibroadenoma										X				X	X			X					X		
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma, metastatic																	X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	−	+
Endometrial stromal polyp	X	X																				X	X		
Deciduoma																									
Ovary	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Zymbal 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											
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, mononuclear cell				X		X									X			X	X			X	X	X	

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

ANIMAL NUMBER	028	031	001	004	006	007	010	012	013	015	016	019	022	024	025	027	030	032	034	035	037	038	041	043	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibroma																				X						1
Neurilemoma, malignant	X	X						X	X									X								9
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																						1
Alveolar/bronchiolar carcinoma														X												1
Neurilemoma, metastatic																										1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Nasal cavity	–	–	–	+	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	–	–	–	+	–	14
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, metastatic																										1
Lymph nodes	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma													X													1
Salivary gland	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	10
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Stomach	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
Fibrosarcoma																										1
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Rectum	N	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
Neurilemoma, metastatic																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma	X																									1
Lipoma						X																				1
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X		X								X		X		X			X	X	X		X			X	21
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma				X																						1
C-cell adenoma									X									X							X	4
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	N	N	N	N	N	N	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	N	*50
Fibroadenoma		X								X	X	X	X	X	X		X	X			X	X	X	X		18
Vagina	N	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
Neurilemoma, metastatic																										1
Uterus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	45
Endometrial stromal polyp													X					X								6
Deciduoma					X																					1
Ovary	–	–	–	+	–	+	–	–	–	–	+	–	–	–	+	–	+	–	–	–	–	–	–	–	+	16
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
SPECIAL SENSE ORGANS																										
Zymbal 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																										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, mononuclear cell	X			X			X		X						X							X			X	15

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: HIGH DOSE

ANIMAL NUMBER	047	009	036	046	013	022	002	040	014	024	029	049	020	037	017	028	018	034	045	044	048	027	032	004	023
WEEKS ON STUDY	001	002	002	010	040	057	066	075	076	081	082	082	085	086	087	089	090	090	090	091	093	096	100	101	101
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																	X								
Fibrosarcoma																									X
Neurilemoma, malignant														X		X					X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								X	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	−	−	−	+	+	−	−	+	+	−	−	+	−	+	+	−	+	+	+
Malignant lymphoma, histiocytic type																									X
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma										X															
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	−	+
Liver	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Bile duct	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell carcinoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									X
Small intestine	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									X
Urinary bladder	+	−	+	+	−	+	−	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS													X											X	
Adrenal	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																							X		
C-cell adenoma																								X	
Parathyroid	+	+	+	+	−	−	−	−	−	+	+	+	+	+	+	−	−	+	+	+	+	−	+	+	−
Pancreatic islets	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	+	N	+	N	N	N	N	+	+	+	+	+	N	+	+	N	+	+	+	+	+
Fibroadenoma												X				X		X	X						
Uterus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Endometrial stromal polyp																	X						X		
Ovary	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal 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
Neoplasm, malignant, 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
Leukemia, mononuclear cell							X		X		X		X						X			X	X		
Site unknown																									
Squamous cell papilloma																					X				

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

ANIMAL NUMBER	0 0 1	0 0 3	0 0 5	0 0 6	0 0 7	0 0 8	0 1 0	0 1 1	0 1 2	0 1 5	0 1 6	0 1 9	0 2 1	0 2 5	0 2 6	0 3 0	0 3 1	0 3 3	0 3 5	0 3 8	0 3 9	0 4 1	0 4 2	0 4 3	0 5 0	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma							X																		2
Fibrosarcoma																									1
Neurilemoma, malignant																									3
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma						X								X											3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																									1
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	–	–	+	–	+	–	–	+	+	–	+	–	+	+	+	–	+	+	+	–	+	–	+	31
Malignant lymphoma, histiocytic type																									1
CIRCULATORY SYSTEM																									
Heart	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma									X														X		3
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																					X				1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell carcinoma						X																			1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																									1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma												X			X								X		4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X	X						X	X				X		X	X				X	X	X			12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary adenoma														X				X							3
C-cell adenoma	X					X				X					X										5
Parathyroid	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma						X																			1
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma	X	X		X	X	X		X	X				X			X	X	X	X				X		17
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma		X																							1
Endometrial stromal polyp						X																			3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																									
Zymbal 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
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	*50
Neoplasm, malignant, 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
Leukemia, mononuclear cell	X				X			X			X	X				X	X					X	X	X	X	18
Site unknown																									
Squamous cell papilloma																									1

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle Control	60 mg/kg	120 mg/kg
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	4.4%	4.3%	10.3%
Terminal Rates (c)	0/27 (0%)	1/23 (4%)	1/25 (4%)
Week of First Observation	86	104	90
Life Table Tests (d)	P=0.348	P=0.532N	P=0.432
Incidental Tumor Tests (d)	P=0.430	P=0.487N	P=0.535
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.500N	P=0.500
Subcutaneous Tissue: Malignant Neurilemoma			
Overall Rates (a)	1/50 (2%)	9/50 (18%)	3/50 (6%)
Adjusted Rates (b)	3.4%	27.9%	8.6%
Terminal Rates (c)	0/27 (0%)	3/23 (13%)	0/25 (0%)
Week of First Observation	102	91	86
Life Table Tests (d)	P=0.216	P=0.008	P=0.240
Incidental Tumor Tests (d)	P=0.218	P=0.011	P=0.213
Cochran-Armitage Trend Test (d)	P=0.297		
Fisher Exact Test (d)		P=0.008	P=0.309
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (e)	0/50 (0%)	1/50 (2%)	3/49 (6%)
Adjusted Rates (b)	0.0%	4.3%	11.4%
Terminal Rates (c)	0/27 (0%)	1/23 (4%)	2/25 (8%)
Week of First Observation		104	101
Life Table Tests (d)	P=0.055	P=0.468	P=0.108
Incidental Tumor Tests (d)	P=0.037	P=0.468	P=0.065
Cochran-Armitage Trend Test (d)	P=0.058		
Fisher Exact Test (d)		P=0.500	P=0.117
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (e)	0/50 (0%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	0.0%	8.7%	11.4%
Terminal Rates (c)	0/27 (0%)	2/23 (9%)	2/25 (8%)
Week of First Observation		104	101
Life Table Tests (d)	P=0.074	P=0.203	P=0.108
Incidental Tumor Tests (d)	P=0.054	P=0.203	P=0.065
Cochran-Armitage Trend Test (d)	P=0.079		
Fisher Exact Test (d)		P=0.247	P=0.117
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	19/50 (38%)	15/50 (30%)	18/50 (36%)
Adjusted Rates (b)	51.6%	44.4%	54.2%
Terminal Rates (c)	10/27 (37%)	6/23 (26%)	11/25 (44%)
Week of First Observation	88	76	66
Life Table Tests (d)	P=0.454	P=0.423N	P=0.485
Incidental Tumor Tests (d)	P=0.350	P=0.268N	P=0.412
Cochran-Armitage Trend Test (d)	P=0.458N		
Fisher Exact Test (d)		P=0.264N	P=0.500N
Heart: Malignant Neurilemoma			
Overall Rates (e)	3/49 (6%)	0/50 (0%)	0/49 (0%)
Adjusted Rates (b)	11.1%	0.0%	0.0%
Terminal Rates (c)	3/27 (11%)	0/23 (0%)	0/24 (0%)
Week of First Observation	104		
Life Table Tests (d)	P=0.047N	P=0.149N	P=0.141N
Incidental Tumor Tests (d)	P=0.047N	P=0.149N	P=0.141N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.117N	P=0.121N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Tongue: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	4.3%	10.2%
Terminal Rates (c)	0/27 (0%)	1/23 (4%)	2/25 (8%)
Week of First Observation		104	81
Life Table Tests (d)	P=0.055	P=0.468	P=0.106
Incidental Tumor Tests (d)	P=0.070	P=0.468	P=0.138
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Oral Cavity: Squamous Cell Papilloma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	3.7%	4.3%	10.2%
Terminal Rates (c)	1/27 (4%)	1/23 (4%)	2/25 (8%)
Week of First Observation	104	104	81
Life Table Tests (d)	P=0.183	P=0.726	P=0.274
Incidental Tumor Tests (d)	P=0.213	P=0.726	P=0.324
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.753	P=0.309
Kidney: Tubular Cell Adenocarcinoma			
Overall Rates (e)	0/50 (0%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	0.0%	4.0%	15.3%
Terminal Rates (c)	0/27 (0%)	0/23 (0%)	3/25 (12%)
Week of First Observation		103	101
Life Table Tests (d)	P=0.023	P=0.477	P=0.054
Incidental Tumor Tests (d)	P=0.009	P=0.515	P=0.032
Cochran-Armitage Trend Test (d)	P=0.026		
Fisher Exact Test (d)		P=0.500	P=0.059
Pituitary Gland: Adenoma			
Overall Rates (e)	19/49 (39%)	21/50 (42%)	12/48 (25%)
Adjusted Rates (b)	58.2%	56.7%	43.7%
Terminal Rates (c)	13/26 (50%)	9/23 (39%)	10/25 (40%)
Week of First Observation	88	56	85
Life Table Tests (d)	P=0.168N	P=0.296	P=0.146N
Incidental Tumor Tests (d)	P=0.157N	P=0.442	P=0.176N
Cochran-Armitage Trend Test (d)	P=0.096N		
Fisher Exact Test (d)		P=0.451	P=0.108N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (e)	20/49 (41%)	21/50 (42%)	12/48 (25%)
Adjusted Rates (b)	59.1%	56.7%	43.7%
Terminal Rates (c)	13/26 (50%)	9/23 (39%)	10/25 (40%)
Week of First Observation	83	56	85
Life Table Tests (d)	P=0.129N	P=0.361	P=0.111N
Incidental Tumor Tests (d)	P=0.106N	P=0.528	P=0.116N
Cochran-Armitage Trend Test (d)	P=0.066N		
Fisher Exact Test (d)		P=0.534	P=0.075N
Thyroid Gland: Papillary Adenoma			
Overall Rates (e)	1/48 (2%)	0/48 (0%)	3/49 (6%)
Adjusted Rates (b)	3.8%	0.0%	11.3%
Terminal Rates (c)	1/26 (4%)	0/23 (0%)	2/25 (8%)
Week of First Observation	104		100
Life Table Tests (d)	P=0.165	P=0.524N	P=0.281
Incidental Tumor Tests (d)	P=0.129	P=0.524N	P=0.217
Cochran-Armitage Trend Test (d)	P=0.181		
Fisher Exact Test (d)		P=0.500N	P=0.316

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Thyroid Gland: Papillary Adenoma or Follicular Cell Adenoma			
Overall Rates (e)	1/48 (2%)	1/48 (2%)	3/49 (6%)
Adjusted Rates (b)	3.8%	4.3%	11.3%
Terminal Rates (c)	1/26 (4%)	1/23 (4%)	2/25 (8%)
Week of First Observation	104	104	100
Life Table Tests (d)	P=0.188	P=0.735	P=0.281
Incidental Tumor Tests (d)	P=0.154	P=0.735	P=0.217
Cochran-Armitage Trend Test (d)	P=0.207		
Fisher Exact Test (d)		P=0.753	P=0.316
Thyroid Gland: C-Cell Adenoma			
Overall Rates (e)	8/48 (17%)	4/48 (8%)	5/49 (10%)
Adjusted Rates (b)	28.8%	15.2%	19.1%
Terminal Rates (c)	7/26 (27%)	3/23 (13%)	4/25 (16%)
Week of First Observation	93	91	101
Life Table Tests (d)	P=0.253N	P=0.231N	P=0.314N
Incidental Tumor Tests (d)	P=0.262N	P=0.223N	P=0.390N
Cochran-Armitage Trend Test (d)	P=0.204N		
Fisher Exact Test (d)		P=0.178N	P=0.263N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (e)	9/48 (19%)	4/48 (8%)	5/49 (10%)
Adjusted Rates (b)	30.9%	15.2%	19.1%
Terminal Rates (c)	7/26 (27%)	3/23 (13%)	4/25 (16%)
Week of First Observation	93	91	101
Life Table Tests (d)	P=0.175N	P=0.163N	P=0.232N
Incidental Tumor Tests (d)	P=0.195N	P=0.148N	P=0.330N
Cochran-Armitage Trend Test (d)	P=0.132N		
Fisher Exact Test (d)		P=0.116N	P=0.182N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	16/50 (32%)	18/50 (36%)	17/50 (34%)
Adjusted Rates (b)	48.9%	60.4%	57.2%
Terminal Rates (c)	11/27 (41%)	12/23 (52%)	13/25 (52%)
Week of First Observation	82	91	82
Life Table Tests (d)	P=0.309	P=0.247	P=0.358
Incidental Tumor Tests (d)	P=0.265	P=0.301	P=0.359
Cochran-Armitage Trend Test (d)	P=0.458		
Fisher Exact Test (d)		P=0.417	P=0.500
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	17/50 (34%)	18/50 (36%)	17/50 (34%)
Adjusted Rates (b)	52.1%	60.4%	57.2%
Terminal Rates (c)	12/27 (44%)	12/23 (52%)	13/25 (52%)
Week of First Observation	82	91	82
Life Table Tests (d)	P=0.384	P=0.311	P=0.437
Incidental Tumor Tests (d)	P=0.341	P=0.375	P=0.443
Cochran-Armitage Trend Test (d)	P=0.542		
Fisher Exact Test (d)		P=0.500	P=0.583
Clitoral Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	8.2%	0.0%	0.0%
Terminal Rates (c)	1/27 (4%)	0/23 (0%)	0/25 (0%)
Week of First Observation	86		
Life Table Tests (d)	P=0.051N	P=0.143N	P=0.159N
Incidental Tumor Tests (d)	P=0.041N	P=0.121N	P=0.147N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	7/50 (14%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	23.6%	18.4%	10.2%
Terminal Rates (c)	5/27 (19%)	2/23 (9%)	1/25 (4%)
Week of First Observation	98	56	90
Life Table Tests (d)	P=0.184N	P=0.584N	P=0.216N
Incidental Tumor Tests (d)	P=0.194N	P=0.447N	P=0.285N
Cochran-Armitage Trend Test (d)	P=0.128N		
Fisher Exact Test (d)		P=0.500N	P=0.159N
All Sites: Benign Tumors			
Overall Rates (a)	37/50 (74%)	41/50 (82%)	30/50 (60%)
Adjusted Rates (b)	92.3%	92.8%	85.3%
Terminal Rates (c)	24/27 (89%)	20/23 (87%)	20/25 (80%)
Week of First Observation	82	56	81
Life Table Tests (d)	P=0.364N	P=0.107	P=0.348N
Incidental Tumor Tests (d)	P=0.271N	P=0.170	P=0.355N
Cochran-Armitage Trend Test (d)	P=0.074N		
Fisher Exact Test (d)		P=0.235	P=0.101N
All Sites: Malignant Tumors			
Overall Rates (a)	27/50 (54%)	24/50 (48%)	28/50 (56%)
Adjusted Rates (b)	62.2%	61.3%	71.2%
Terminal Rates (c)	11/27 (41%)	9/23 (39%)	14/25 (56%)
Week of First Observation	75	75	66
Life Table Tests (d)	P=0.263	P=0.542N	P=0.287
Incidental Tumor Tests (d)	P=0.173	P=0.269N	P=0.160
Cochran-Armitage Trend Test (d)	P=0.460		
Fisher Exact Test (d)		P=0.345N	P=0.500
All Sites: All Tumors			
Overall Rates (a)	46/50 (92%)	48/50 (96%)	42/50 (84%)
Adjusted Rates (b)	95.8%	97.9%	97.7%
Terminal Rates (c)	25/27 (93%)	22/23 (96%)	24/25 (96%)
Week of First Observation	75	56	66
Life Table Tests (d)	P=0.420	P=0.185	P=0.469
Incidental Tumor Tests (d)	P=0.562	P=0.458	P=0.539
Cochran-Armitage Trend Test (d)	P=0.114N		
Fisher Exact Test (d)		P=0.339	P=0.179N

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

TABLE B4a. HISTORICAL INCIDENCE OF KIDNEY TUBULAR CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Adenomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	0/50
Ampicillin trihydrate	(b) 1/50
Penicillin VK	0/49
TOTAL	1/149 (0.7%)
SD (c)	1.15%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 2/2,094 (0.1%)
SD (c)	0.43%
Range (d)	
High	1/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Adenoma, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one adenoma, NOS, and one tubular cell adenoma; no malignant tumors have been observed.

TABLE B4b. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Neurilemomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	(b) 2/50
Ampicillin trihydrate	0/50
Penicillin VK	0/50
TOTAL	2/150 (1.3%)
SD (c)	2.31%
Range (d)	
High	2/50
Low	0/50
Overall Historical Incidence	
TOTAL	(b) 3/2,100 (0.1%)
SD (c)	0.68%
Range (d)	
High	2/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes one malignant neurilemoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B4c. HISTORICAL INCIDENCE OF ORAL CAVITY SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	(b) 1/50
Ampicillin trihydrate	0/50
Penicillin VK	0/50
TOTAL	1/150 (0.7%)
SD (c)	1.15%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 7/2,100 (0.3%)
SD (c)	0.87%
Range (d)	
High	2/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks; unless otherwise specified, entries refer to squamous cell papillomas of the tongue (no malignant tumors have been observed).
(b) Papilloma, NOS, of the tongue
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one squamous cell papilloma of the palate

TABLE B4d. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	0/50
Ampicillin trihydrate	0/49
Penicillin VK	0/49
TOTAL	0/148
SD (b)	0.00%
Range (c)	
High	0/50
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 9/2,085 (0.4%)
SD (b)	0.95%
Range (c)	
High	2/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes seven squamous cell papillomas, one papilloma, NOS, and one squamous cell carcinoma

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, acute diffuse			1 (2%)
Granuloma, foreign body		1 (2%)	
RESPIRATORY SYSTEM			
#Nose	(49)	(14)	(49)
Inflammation, acute focal		1 (7%)	1 (2%)
Inflammation, acute/chronic	1 (2%)		1 (2%)
Inflammation, chronic	1 (2%)		
Degeneration, hyaline	34 (69%)	10 (71%)	19 (39%)
#Nasal gland	(49)	(14)	(49)
Fibrosis	1 (2%)		
#Trachea	(49)	(10)	(50)
Inflammation, acute		1 (10%)	
Inflammation, chronic	1 (2%)		
#Tracheal gland	(49)	(10)	(50)
Inflammation, acute	1 (2%)		
#Lung/bronchiole	(50)	(50)	(49)
Hyperplasia, focal		1 (2%)	
#Lung	(50)	(50)	(49)
Congestion, NOS	1 (2%)	2 (4%)	4 (8%)
Edema, NOS			1 (2%)
Hemorrhage	1 (2%)		3 (6%)
Inflammation, interstitial			2 (4%)
Pneumonia, aspiration			1 (2%)
Bronchopneumonia, acute		1 (2%)	
Inflammation, chronic	2 (4%)	3 (6%)	4 (8%)
Perivascular cuffing	19 (38%)	4 (8%)	15 (31%)
Deposit, NOS			1 (2%)
Alveolar macrophages	3 (6%)	1 (2%)	6 (12%)
Hyperplasia, adenomatous	2 (4%)	4 (8%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemoid reaction	1 (2%)		
*Blood	(50)	(50)	(50)
Leukocytosis, NOS	4 (8%)	1 (2%)	1 (2%)
#Bone marrow	(50)	(9)	(50)
Fibrosis, focal	1 (2%)		
Metaplasia, osseous	1 (2%)		
Hyperplasia, hematopoietic		1 (11%)	
Hyperplasia, granulocytic	3 (6%)		2 (4%)
#Spleen	(50)	(50)	(49)
Inflammation, granulomatous focal			1 (2%)
Fibrosis, diffuse	1 (2%)		
Infarct, NOS	1 (2%)		
Hemosiderosis	10 (20%)	16 (32%)	17 (35%)
Hematopoiesis	5 (10%)	4 (8%)	5 (10%)
Erythropoiesis		2 (4%)	1 (2%)
#Splenic capsule	(50)	(50)	(49)
Sclerosis			1 (2%)
#Lymph node	(50)	(11)	(48)
Plasmacytosis	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Submandibular lymph node	(50)	(11)	(48)
Hemosiderosis	1 (2%)		1 (2%)
Hyperplasia, lymphoid			1 (2%)
#Mesenteric lymph node	(50)	(11)	(48)
Hyperplasia, lymphoid		1 (9%)	
#Renal lymph node	(50)	(11)	(48)
Hyperplasia, lymphoid		1 (9%)	
#Liver	(50)	(50)	(49)
Hematopoiesis		2 (4%)	1 (2%)
#Liver/kupffer cell	(50)	(50)	(49)
Erythrophagocytosis			1 (2%)
#Jejunum	(50)	(9)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Adrenal cortex	(50)	(9)	(49)
Hematopoiesis			1 (2%)
#Thymus	(34)	(6)	(31)
Hemorrhage			1 (3%)
CIRCULATORY SYSTEM			
#Submandibular lymph node	(50)	(11)	(48)
Lymphangiectasis	1 (2%)		
#Myocardium	(49)	(50)	(49)
Inflammation, chronic	8 (16%)	3 (6%)	11 (22%)
Fibrosis	12 (24%)	8 (16%)	5 (10%)
*Artery	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
*Pulmonary artery	(50)	(50)	(50)
Mineralization	4 (8%)	13 (26%)	
*Hepatic artery	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
*Mesentery	(50)	(50)	(50)
Periarteritis			1 (2%)
#Uterus	(49)	(45)	(49)
Thrombus, organized		1 (2%)	
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Hyperplasia, pseudoepitheliomatous	1 (2%)		
*Tongue	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	1 (2%)
Hyperkeratosis		1 (2%)	
#Salivary gland	(49)	(10)	(45)
Inflammation, acute	1 (2%)	1 (10%)	1 (2%)
Inflammation, chronic	1 (2%)		2 (4%)
Fibrosis, focal			1 (2%)
Focal cellular change	1 (2%)		
Cytologic alteration, NOS			1 (2%)
Atrophy, focal	2 (4%)		2 (4%)
Hyperplasia, NOS			1 (2%)
#Liver	(50)	(50)	(49)
Hernia, NOS	4 (8%)	2 (4%)	4 (8%)
Congestion, NOS		2 (4%)	3 (6%)
Lymphocytic inflammatory infiltrate	2 (4%)		1 (2%)
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic			2 (4%)
Inflammation, granulomatous focal	1 (2%)	1 (2%)	1 (2%)
Cholangiofibrosis			1 (2%)
Degeneration, NOS	8 (16%)	6 (12%)	8 (16%)
Necrosis, focal	1 (2%)	5 (10%)	1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(50)	(49)
Metamorphosis, fatty	2 (4%)	7 (14%)	2 (4%)
Mitotic alteration		1 (2%)	
Focal cellular change	39 (78%)	11 (22%)	22 (45%)
Clear cell change		1 (2%)	1 (2%)
Hyperplasia, nodular	1 (2%)	2 (4%)	2 (4%)
Angiectasis		2 (4%)	1 (2%)
#Intrahepatic bile duct	(50)	(50)	(49)
Inflammation, chronic	2 (4%)	4 (8%)	2 (4%)
Inflammation, granulomatous focal	1 (2%)		
Hyperplasia, NOS	18 (36%)	6 (12%)	8 (16%)
#Liver/centrilobular	(50)	(50)	(49)
Degeneration, NOS			4 (8%)
Necrosis, NOS		1 (2%)	
Metamorphosis, fatty			2 (4%)
Cytoplasmic vacuolization			2 (4%)
Atrophy, NOS		1 (2%)	
#Liver/periportal	(50)	(50)	(49)
Metamorphosis, fatty	2 (4%)	2 (4%)	2 (4%)
#Liver/hepatocytes	(50)	(50)	(49)
Pleomorphism		1 (2%)	
Atypia, NOS	1 (2%)		
#Pancreas	(50)	(50)	(49)
Inflammation, chronic focal	1 (2%)		
Focal cellular change			1 (2%)
Atrophy, focal	17 (34%)	9 (18%)	10 (20%)
Hyperplasia, nodular	3 (6%)	3 (6%)	
#Esophagus	(48)	(9)	(50)
Hyperkeratosis			1 (2%)
#Gastric mucosa	(50)	(13)	(49)
Cyst, NOS		1 (8%)	
Ulcer, NOS	3 (6%)		2 (4%)
Inflammation, acute/chronic			1 (2%)
Hyperkeratosis		2 (15%)	1 (2%)
#Glandular stomach	(50)	(13)	(49)
Ulcer, NOS		1 (8%)	
Erosion			1 (2%)
Fibrosis, diffuse	1 (2%)		
Hyperplasia, epithelial		1 (8%)	
#Gastric submucosa	(50)	(13)	(49)
Edema, NOS	1 (2%)		
Eosinophilic leukocytic infiltrate	1 (2%)		
Inflammation, chronic		2 (15%)	2 (4%)
#Gastric muscularis	(50)	(13)	(49)
Inflammation, acute/chronic		1 (8%)	
#Forestomach	(50)	(13)	(49)
Edema, NOS		1 (8%)	1 (2%)
Ulcer, NOS		2 (15%)	1 (2%)
Inflammation, chronic		1 (8%)	1 (2%)
Hyperplasia, epithelial		3 (23%)	3 (6%)
#Colon	(50)	(9)	(49)
Parasitism	9 (18%)		10 (20%)
*Rectum	(50)	(50)	(50)
Inflammation, acute	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hydronephrosis	1 (2%)		
Cyst, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	1 (2%)
Nephropathy	29 (58%)	48 (96%)	39 (78%)
Infarct, focal	1 (2%)		6 (12%)
Hyperplasia, atypical		1 (2%)	3 (6%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS		1 (2%)	1 (2%)
#Kidney/glomerulus	(50)	(50)	(50)
Amyloidosis			2 (4%)
#Kidney/tubule	(50)	(50)	(50)
Metamorphosis, fatty	2 (4%)	2 (4%)	
Pigmentation, NOS	3 (6%)	8 (16%)	6 (12%)
#Kidney/pelvis	(50)	(50)	(50)
Hyperplasia, papillary		1 (2%)	
#Urinary bladder	(46)	(8)	(44)
Edema, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(49)	(50)	(48)
Cyst, NOS	22 (45%)	17 (34%)	15 (31%)
Hemorrhagic cyst	2 (4%)		
Hemosiderosis	1 (2%)	1 (2%)	
Hyperplasia, chromophobe cell	12 (24%)	9 (18%)	12 (25%)
Angiectasis	1 (2%)	1 (2%)	2 (4%)
#Adrenal	(50)	(9)	(49)
Congestion, NOS			2 (4%)
Necrosis, focal	1 (2%)		
#Adrenal cortex	(50)	(9)	(49)
Ectopia	2 (4%)		5 (10%)
Metamorphosis, fatty	8 (16%)	4 (44%)	2 (4%)
Focal cellular change		1 (11%)	
Hyperplasia, nodular	12 (24%)	3 (33%)	15 (31%)
#Adrenal medulla	(50)	(9)	(49)
Hyperplasia, focal			2 (4%)
#Thyroid	(48)	(48)	(49)
Cystic follicles	4 (8%)	2 (4%)	
Hyperplasia, C-cell	10 (21%)	9 (19%)	4 (8%)
#Thyroid follicle	(48)	(48)	(49)
Metaplasia, squamous	1 (2%)		1 (2%)
#Parathyroid	(33)	(7)	(38)
Fibrosis	1 (3%)		
Hyperplasia, nodular			1 (3%)
#Pancreatic islets	(50)	(50)	(49)
Cytologic alteration, NOS		1 (2%)	
Metaplasia, NOS		1 (2%)	11 (22%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts		1 (2%)	
Inflammation, acute/chronic	2 (4%)		
Inflammation, chronic focal	1 (2%)		
Fibrosis, diffuse		1 (2%)	
Hyperplasia, cystic	25 (50%)	15 (30%)	20 (40%)
*Preputial gland	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
*Clitoral gland	(50)	(50)	(50)
Cyst, NOS	1 (2%)	1 (2%)	
Inflammation, acute		2 (4%)	
Inflammation, acute/chronic	6 (12%)	2 (4%)	4 (8%)
Inflammation, chronic	16 (32%)	7 (14%)	17 (34%)
Degeneration, cystic	1 (2%)		1 (2%)
Hyperplasia, cystic			1 (2%)
*Vagina	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		
#Uterus	(49)	(45)	(49)
Dilatation, NOS	12 (24%)	4 (9%)	1 (2%)
Epidermal inclusion cyst		1 (2%)	
Hyperplasia, stromal		1 (2%)	
#Uterus/endometrium	(49)	(45)	(49)
Hyperplasia, cystic			1 (2%)
Metaplasia, squamous			1 (2%)
#Endometrial gland	(49)	(45)	(49)
Cyst, NOS	1 (2%)	2 (4%)	
Degeneration, cystic	1 (2%)		
#Ovary	(50)	(16)	(49)
Cyst, NOS	1 (2%)	2 (13%)	2 (4%)
#Mesovarium	(50)	(16)	(49)
Necrosis, fat	5 (10%)	5 (31%)	2 (4%)
Angiectasis	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(9)	(49)
Hydrocephalus, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	7 (14%)	1 (2%)	
*Eye/lens, cortex	(50)	(50)	(50)
Cataract	7 (14%)	3 (6%)	
*Nasolacrimal duct	(50)	(50)	(50)
Epidermal inclusion cyst			1 (2%)
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	18 (36%)	6 (12%)	24 (48%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteosclerosis	13 (26%)		9 (18%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage			1 (2%)
Necrosis, fat		1 (2%)	
*Mesentery	(50)	(50)	(50)
Necrosis, fat	6 (12%)	6 (12%)	5 (10%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Edema, NOS			1 (2%)
Hemorrhage			1 (2%)
Site unknown			
Inflammation, acute diffuse	1		
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle 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)
Keratoacanthoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)		1 (2%)
Fibrosarcoma	2 (4%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Hepatocellular carcinoma, metastatic	4 (8%)	2 (4%)	2 (4%)
Alveolar/bronchiolar adenoma	4 (8%)	7 (14%)	15 (31%)
Alveolar/bronchiolar carcinoma	7 (14%)	3 (6%)	5 (10%)
Hepatoblastoma, metastatic		1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type			3 (6%)
Malignant lymphoma, mixed type	1 (2%)	1 (2%)	2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Malignant lymphoma, mixed type	1 (2%)		
#Spleen	(50)	(29)	(50)
Squamous cell carcinoma, metastatic		1 (3%)	1 (2%)
#Lymph node	(49)	(19)	(46)
Squamous cell carcinoma, metastatic		1 (5%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(23)	(50)
Hepatoblastoma, metastatic		1 (4%)	
#Myocardium	(50)	(23)	(50)
Neurilemoma			1 (2%)
#Liver	(50)	(49)	(50)
Hemangiosarcoma	2 (4%)		1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(50)
Squamous cell carcinoma, metastatic		1 (2%)	
Hepatocellular adenoma	4 (8%)	24 (49%)	34 (68%)
Hepatocellular carcinoma	9 (18%)	8 (16%)	9 (18%)
Hepatoblastoma		3 (6%)	18 (36%)
#Hepatic capsule	(50)	(49)	(50)
Squamous cell carcinoma, invasive		1 (2%)	
#Glandular stomach	(50)	(49)	(50)
Squamous cell carcinoma, invasive			2 (4%)
#Forestomach	(50)	(49)	(50)
Squamous cell papilloma	2 (4%)	7 (14%)	10 (20%)
Squamous cell carcinoma		4 (8%)	3 (6%)
#Jejunum	(50)	(22)	(50)
Adenocarcinoma, NOS	1 (2%)	2 (9%)	
#Ileum	(50)	(22)	(50)
Adenocarcinoma, NOS	1 (2%)	1 (5%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hepatoblastoma, metastatic		1 (2%)	
#Kidney/capsule	(50)	(50)	(50)
Squamous cell carcinoma, metastatic			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(47)	(13)	(42)
Chromophobe adenoma	1 (2%)		
#Adrenal	(49)	(46)	(45)
Cortical adenoma		2 (4%)	1 (2%)
#Adrenal/capsule	(49)	(46)	(45)
Squamous cell carcinoma, metastatic			1 (2%)
Adenoma, NOS		1 (2%)	1 (2%)
#Adrenal medulla	(49)	(46)	(45)
Pheochromocytoma			1 (2%)
#Pancreatic islets	(50)	(19)	(48)
Islet cell adenoma	1 (2%)		
REPRODUCTIVE SYSTEM			
#Testis	(50)	(24)	(50)
Interstitial cell tumor		1 (4%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)		3 (6%)
MUSCULOSKELETAL SYSTEM			
*Rib	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
*Skeletal muscle	(50)	(50)	(50)
Hepatoblastoma, metastatic		1 (2%)	
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Squamous cell carcinoma, invasive		1 (2%)	
*Pleura	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive			1 (2%)
Hepatoblastoma, metastatic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
Hepatoblastoma, metastatic			1 (2%)
Orbital region			
Sarcoma, NOS	1		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	8	10	16
Moribund sacrifice	8	7	4
Terminal sacrifice	33	20	27
Dosing accident	1	13	3
TUMOR SUMMARY			
Total animals with primary tumors**	29	32	45
Total primary tumors	40	66	108
Total animals with benign tumors	12	27	42
Total benign tumors	15	43	67
Total animals with malignant tumors	21	16	33
Total malignant tumors	25	23	41
Total animals with secondary tumors##	4	6	9
Total secondary tumors	4	12	12

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: VEHICLE CONTROL

ANIMAL NUMBER	0229	0230	0115	0114	0116	0223	0222	0242	0009	0037	0001	0445	0006	0008	0111	0444	0048	0002	0003	0004	0005	0007	0110	0112	0113
WEEKS ON STUDY	015	043	080	083	085	086	090	091	093	094	099	099	101	101	101	101	102	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																						X			
Fibrosarcoma											X		X												
Malignant lymphoma, mixed type																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic			X					X								X									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma					X				X						X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	–	–	+	–	–	–	+	–	–	–	+	–	+	+	–	+	+	–	+	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X			X	
Hepatocellular carcinoma			X					X				X			X	X	X								
Hemangiosarcoma									X																
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	N	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Chromophobe adenoma																									
Adrenal	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–
Parathyroid	–	–	+	+	+	+	–	–	+	–	–	–	+	–	+	+	–	+	+	+	+	–	+	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									X
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, mixed type																									
Orbital region																									
Sarcoma, NOS															X										

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0 1 7	0 1 8	0 1 9	0 2 1	0 2 4	0 2 5	0 2 6	0 2 7	0 2 8	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 8	0 3 9	0 4 0	0 4 1	0 4 3	0 4 6	0 4 7	0 4 9	0 5 0	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Fibroma																									1	
Fibrosarcoma																									2	
Malignant lymphoma, mixed type						X																			1	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular carcinoma, metastatic											X														4	
Alveolar/bronchiolar adenoma						X			X												X	X			4	
Alveolar/bronchiolar carcinoma												X		X							X	X			7	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48	
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Thymus	+	–	+	+	+	–	+	+	+	–	+	–	–	+	+	+	+	–	–	+	–	–	+	–	24	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular adenoma																						X			4	
Hepatocellular carcinoma											X								X			X			9	
Hemangiosarcoma																								X	2	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Squamous cell papilloma									X											X					2	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenocarcinoma, NOS					X																	X			2	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Chromophobe adenoma														X											1	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	45	
Parathyroid	–	+	+	+	+	+	–	–	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	+	33	
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Islet cell adenoma																									1	
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	*50	
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50	
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	*50	
Malignant lymphoma, mixed type		X																							1	
Orbital region																										
Sarcoma, NOS																									1	

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: LOW DOSE

ANIMAL NUMBER	0023	0004	0007	0008	0009	0020	0022	0039	0042	0040	0041	0001	0005	0035	0014	0047	0003	0025	0011	0006	0049	0027	0030	0024	0032
WEEKS ON STUDY	0007	0020	0020	0020	0020	0020	0020	0020	0020	0021	0021	0035	0035	0061	0063	0078	0081	0081	0083	0086	0088	0089	0089	0091	0091
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Keratoacanthoma																									X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																			X	X					
Alveolar/bronchiolar adenoma																	X	X							
Alveolar/bronchiolar carcinoma																									
Hepatoblastoma, metastatic																X									
Trachea	−	−	+	+	+	−	−	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	−	−	+	+	+	−	−	−	+	+	+	−	+	+	+	−	+	+	+	−	+	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Lymph nodes	−	−	−	+	+	+	+	−	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	−
Squamous cell carcinoma, metastatic																									
Thymus	−	+	+	+	+	+	+	−	+	−	−	+	−	+	+	+	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
Hepatoblastoma, metastatic																X									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
Liver	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																					X				
Squamous cell carcinoma, metastatic																									
Hepatocellular adenoma																		X		X	X			X	X
Hepatocellular carcinoma																X			X	X		X	X		
Hepatoblastoma																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
Pancreas	+	+	+	+	+	+	−	−	−	+	+	+	+	+	−	+	+	+	+	+	−	+	−	−	−
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	+	+	−	−
Stomach	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Squamous cell carcinoma																					X		X		
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	−
Adenocarcinoma, NOS																				X					
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic																X									
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	−	+	+	−	−	−	+	−	−	−	+	+	+	−	+	+	+	−	−	−	−
Adrenal	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−
Adenoma, NOS																									
Cortical adenoma																						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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
Interstitial cell tumor																									
Prostate	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
MUSCULOSKELETAL SYSTEM																									
Bone	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	+	+	+	N	N	N	N	N	N
Osteosarcoma																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	+	+	+	+	+	+	+	N	N
Hepatoblastoma, metastatic																X									
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatoblastoma, metastatic																X									
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
Squamous cell carcinoma, invasive																							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, mixed type																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	033	031	034	029	015	002	010	012	013	016	017	018	019	021	026	028	036	037	038	043	044	045	046	048	050	TOTAL:
WEEKS ON STUDY	094	095	095	096	100	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	+	N	N	N	+	*50
Keratoacanthoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma	X		X						X				X											X		7
Alveolar/bronchiolar carcinoma					X																X			X		3
Hepatoblastoma, metastatic																										1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	16
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
Spleen	+	–	–	+	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	29
Squamous cell carcinoma, metastatic					X																					1
Lymph nodes	–	–	–	–	+	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19
Squamous cell carcinoma, metastatic					X																					1
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	23
Hepatoblastoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	+	–	25
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, invasive																										1
Squamous cell carcinoma, metastatic					X																					1
Hepatocellular adenoma	X		X		X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X			24
Hepatocellular carcinoma							X	X																X		6
Hepatoblastoma											X															3
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	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	20
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma	X					X				X			X			X	X									7
Squamous cell carcinoma					X														X							4
Small intestine	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	22
Adenocarcinoma, NOS											X						X									3
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	20
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma, metastatic																										1
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	23
ENDOCRINE SYSTEM																										
Pituitary	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS																			X							1
Cortical adenoma																			X							2
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	16
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
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	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	24
Interstitial cell tumor																			X							1
Prostate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	21
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	23
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	*50
Osteosarcoma	X																									1
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatoblastoma, metastatic																										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
Hepatoblastoma, metastatic																										1
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, mixed type											X															1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: HIGH DOSE

ANIMAL NUMBER	0017	0004	0488	0337	0046	0332	0334	0333	0003	0277	0422	0123	0134	0144	0386	0026	0385	0399	0244	0199	0229	0331	0001	0005	0007
WEEKS ON STUDY	0155	0188	0333	0433	0499	0669	0699	0711	0733	0799	0872	0911	0991	0991	0933	0988	0988	0999	1000	1003	1003	1003	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic															X			X							
Alveolar/bronchiolar adenoma							X			X					X					X		X		
Alveolar/bronchiolar carcinoma								X	X													X			
Hepatoblastoma, metastatic																	X								
Trachea	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic															X										
Lymph nodes	–	–	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	–	+	+	–	–	+	–	–	–	–	+	–	–	–	–	+	–	–	–	–	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X	X		X	X	X	X		X		X	X	X	X	X	X	X	
Hepatocellular carcinoma															X		X	X		X					
Hepatoblastoma											X		X		X		X	X	X						
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	N	N	+	N	N	+	+	+	N	+	N	N	+	+	+	+	+	N	+
Pancreas	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																	X	X					X	X	X
Squamous cell carcinoma			X												X										
Squamous cell carcinoma, invasive			X												X										
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic															X										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	–	–	–	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	–	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic															X										
Adenoma, NOS																								X	
Cortical adenoma																									
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	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS													X	X							X				
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, invasive								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
Alveolar/bronchiolar carcinoma, metastatic									X																
Hepatoblastoma, metastatic																									
Malignant lymphoma, lymphocytic type										X		X													X
Malignant lymphoma, mixed type																				X					

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	0008	0009	0110	0111	0115	0116	0118	0220	0221	0223	0225	0226	0228	0229	0330	0338	0440	0441	0443	0444	0445	0446	0447	0449	0550	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																						X				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma						X	X	X		X							X		X		X	X			X	15
Alveolar/bronchiolar carcinoma			X														X									5
Hepatoblastoma, metastatic																							X			2
Trachea	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	−	+	−	−	−	+	+	+	+	−	+	−	+	−	+	−	+	−	−	−	+	+	−	+	+	19
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma			X																							1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X		X		34
Hepatocellular carcinoma		X														X					X	X			X	9
Hepatoblastoma		X		X		X	X			X		X	X		X				X				X	X	X	18
Hemangiosarcoma							X																			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X			X	X			X											X				10
Squamous cell carcinoma						X																				3
Squamous cell carcinoma, invasive																										2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+		49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+		47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adrenal	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Squamous cell carcinoma, metastatic																										1
Adenoma, NOS																										1
Cortical adenoma												X														1
Pheochromocytoma																X										1
Thyroid	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Parathyroid	−	+	−	−	+	+	+	−	+	−	−	+	−	+	+	−	−	−	−	+	+	+	+	−	+	23
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+		48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										3
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, inv																										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
Alveolar/bronchiolar carcinoma, meta																										1
Hepatoblastoma, metastatic										X																1
Malignant lymphoma, lymphocytic type																										3
Malignant lymphoma, mixed type					X																					2

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle Control	60 mg/kg	120 mg/kg
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/49 (6%)	0/39 (0%)	1/48 (2%)
Adjusted Rates (b)	7.9%	0.0%	3.6%
Terminal Rates (c)	1/33 (3%)	0/20 (0%)	1/28 (4%)
Week of First Observation	99		104
Life Table Tests (d)	P=0.241N	P=0.247N	P=0.374N
Incidental Tumor Tests (d)	P=0.227N	P=0.233N	P=0.357N
Cochran-Armitage Trend Test (d)	P=0.188N		
Fisher Exact Test (d)		P=0.168N	P=0.316N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (e)	4/49 (8%)	7/39 (18%)	15/48 (31%)
Adjusted Rates (b)	12.1%	26.4%	44.1%
Terminal Rates (c)	4/33 (12%)	3/20 (15%)	10/28 (36%)
Week of First Observation	104	81	69
Life Table Tests (d)	P=0.002	P=0.072	P=0.002
Incidental Tumor Tests (d)	P=0.002	P=0.101	P=0.003
Cochran-Armitage Trend Test (d)	P=0.003		
Fisher Exact Test (d)		P=0.146	P=0.004
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (e)	7/49 (14%)	3/39 (8%)	5/48 (10%)
Adjusted Rates (b)	18.3%	14.3%	14.3%
Terminal Rates (c)	4/33 (12%)	2/20 (10%)	2/28 (7%)
Week of First Observation	85	100	71
Life Table Tests (d)	P=0.422N	P=0.436N	P=0.487N
Incidental Tumor Tests (d)	P=0.262N	P=0.382N	P=0.228N
Cochran-Armitage Trend Test (d)	P=0.326N		
Fisher Exact Test (d)		P=0.268N	P=0.394N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (e)	10/49 (20%)	9/39 (23%)	19/48 (40%)
Adjusted Rates (b)	26.7%	34.0%	51.3%
Terminal Rates (c)	7/33 (21%)	4/20 (20%)	11/28 (39%)
Week of First Observation	85	81	69
Life Table Tests (d)	P=0.015	P=0.260	P=0.018
Incidental Tumor Tests (d)	P=0.022	P=0.342	P=0.053
Cochran-Armitage Trend Test (d)	P=0.023		
Fisher Exact Test (d)		P=0.481	P=0.032
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	0/49 (0%)	0/39 (0%)	3/48 (6%)
Adjusted Rates (b)	0.0%	0.0%	8.3%
Terminal Rates (c)	0/33 (0%)	0/20 (0%)	1/28 (4%)
Week of First Observation			79
Life Table Tests (d)	P=0.037	(f)	P=0.100
Incidental Tumor Tests (d)	P=0.023	(f)	P=0.087
Cochran-Armitage Trend Test (d)	P=0.041		
Fisher Exact Test (d)		(f)	P=0.117
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	2/49 (4%)	1/39 (3%)	5/48 (10%)
Adjusted Rates (b)	6.1%	5.0%	14.6%
Terminal Rates (c)	2/33 (6%)	1/20 (5%)	2/28 (7%)
Week of First Observation	104	104	79
Life Table Tests (d)	P=0.112	P=0.673N	P=0.170
Incidental Tumor Tests (d)	P=0.101	P=0.673N	P=0.158
Cochran-Armitage Trend Test (d)	P=0.135		
Fisher Exact Test (d)		P=0.586N	P=0.209

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (e)	4/49 (8%)	24/39 (62%)	34/48 (71%)
Adjusted Rates (b)	12.1%	85.3%	84.8%
Terminal Rates (c)	4/33 (12%)	16/20 (80%)	22/28 (79%)
Week of First Observation	104	81	71
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (e)	9/49 (18%)	8/39 (21%)	9/48 (19%)
Adjusted Rates (b)	22.1%	27.9%	27.2%
Terminal Rates (c)	3/33 (9%)	3/20 (15%)	5/28 (18%)
Week of First Observation	80	78	93
Life Table Tests (d)	P=0.407	P=0.305	P=0.460
Incidental Tumor Tests (d)	P=0.471	P=0.548N	P=0.466
Cochran-Armitage Trend Test (d)	P=0.532		
Fisher Exact Test (d)		P=0.505	P=0.584
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (e)	12/49 (24%)	30/39 (77%)	37/48 (77%)
Adjusted Rates (b)	29.8%	93.5%	88.1%
Terminal Rates (c)	6/33 (18%)	18/20 (90%)	23/28 (82%)
Week of First Observation	80	78	71
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Liver: Hepatoblastoma			
Overall Rates (e)	0/49 (0%)	3/39 (8%)	18/48 (38%)
Adjusted Rates (b)	0.0%	10.4%	51.8%
Terminal Rates (c)	0/33 (0%)	1/20 (5%)	12/28 (43%)
Week of First Observation		78	87
Life Table Tests (d)	P<0.001	P=0.066	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.224	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.083	P<0.001
Liver: Hepatocellular Carcinoma or Hepatoblastoma			
Overall Rates (e)	9/49 (18%)	10/39 (26%)	22/48 (46%)
Adjusted Rates (b)	22.1%	34.2%	62.1%
Terminal Rates (c)	3/33 (9%)	4/20 (20%)	15/28 (54%)
Week of First Observation	80	78	87
Life Table Tests (d)	P=0.002	P=0.143	P=0.002
Incidental Tumor Tests (d)	P<0.001	P=0.448	P<0.001
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Test (d)		P=0.286	P=0.003
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma			
Overall Rates (e)	12/49 (24%)	31/39 (79%)	40/48 (83%)
Adjusted Rates (b)	29.8%	96.8%	95.2%
Terminal Rates (c)	6/33 (18%)	19/20 (95%)	26/28 (93%)
Week of First Observation	80	78	71
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	2/49 (4%)	7/39 (18%)	10/48 (21%)
Adjusted Rates (b)	6.1%	30.7%	32.7%
Terminal Rates (c)	2/33 (6%)	5/20 (25%)	8/28 (29%)
Week of First Observation	104	91	98
Life Table Tests (d)	P=0.007	P=0.013	P=0.007
Incidental Tumor Tests (d)	P=0.006	P=0.018	P=0.007
Cochran-Armitage Trend Test (d)	P=0.013		
Fisher Exact Test (d)		P=0.037	P=0.012
Forestomach: Squamous Cell Carcinoma			
Overall Rates (a)	0/49 (0%)	4/39 (10%)	3/48 (6%)
Adjusted Rates (b)	0.0%	15.6%	8.3%
Terminal Rates (c)	0/33 (0%)	1/20 (5%)	1/28 (4%)
Week of First Observation		88	33
Life Table Tests (d)	P=0.107	P=0.022	P=0.106
Incidental Tumor Tests (d)	P=0.122	P=0.050	P=0.161
Cochran-Armitage Trend Test (d)	P=0.120		
Fisher Exact Test (d)		P=0.035	P=0.117
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	2/49 (4%)	11/39 (28%)	13/48 (27%)
Adjusted Rates (b)	6.1%	42.5%	39.3%
Terminal Rates (c)	2/33 (6%)	6/20 (30%)	9/28 (32%)
Week of First Observation	104	88	33
Life Table Tests (d)	P=0.002	P<0.001	P=0.001
Incidental Tumor Tests (d)	P=0.002	P=0.001	P=0.001
Cochran-Armitage Trend Test (d)	P=0.003		
Fisher Exact Test (d)		P=0.002	P=0.002
Harderian Gland: Adenoma			
Overall Rates (a)	2/49 (4%)	0/39 (0%)	3/48 (6%)
Adjusted Rates (b)	5.4%	0.0%	8.2%
Terminal Rates (c)	1/33 (3%)	0/20 (0%)	0/28 (0%)
Week of First Observation	94		91
Life Table Tests (d)	P=0.355	P=0.354N	P=0.448
Incidental Tumor Tests (d)	P=0.338	P=0.365N	P=0.430
Cochran-Armitage Trend Test (d)	P=0.386		
Fisher Exact Test (d)		P=0.307N	P=0.490
All Sites: Benign Tumors			
Overall Rates (a)	12/49 (24%)	27/39 (69%)	42/48 (88%)
Adjusted Rates (b)	35.0%	89.7%	95.5%
Terminal Rates (c)	11/33 (33%)	17/20 (85%)	26/28 (93%)
Week of First Observation	94	81	69
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
All Sites: Malignant Tumors			
Overall Rates (a)	21/49 (43%)	16/39 (41%)	33/48 (69%)
Adjusted Rates (b)	48.3%	52.7%	78.2%
Terminal Rates (c)	11/33 (33%)	7/20 (35%)	19/28 (68%)
Week of First Observation	80	78	33
Life Table Tests (d)	P=0.007	P=0.296	P=0.008
Incidental Tumor Tests (d)	P=0.003	P=0.517N	P=0.004
Cochran-Armitage Trend Test (d)	P=0.007		
Fisher Exact Test (d)		P=0.518N	P=0.009

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
All Sites: All Tumors			
Overall Rates (a)	29/49 (59%)	32/39 (82%)	45/48 (94%)
Adjusted Rates (b)	65.6%	96.9%	100%
Terminal Rates (c)	18/33 (55%)	19/20 (95%)	28/28 (100%)
Week of First Observation	80	78	33
Life Table Tests (d)	P<0.001	P=0.002	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.003	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.018	P<0.001

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined microscopically at the site
(f) No P value is reported because no tumors were observed in the 60 mg/kg and vehicle control groups.

TABLE C4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
N,N-Dimethylaniline	7/50	4/50	11/50
Ampicillin trihydrate	3/50	6/50	9/50
Penicillin VK	14/50	6/50	19/50
TOTAL	24/150 (16.0%)	16/150 (10.7%)	39/150 (26.0%)
SD (b)	11.14%	2.31%	10.58%
Range (c)			
High	14/50	6/50	19/50
Low	3/50	4/50	9/50
Overall Historical Incidence			
TOTAL	325/2,084 (15.6%)	404/2,084 (19.4%)	688/2,084 (33.0%)
SD (b)	7.07%	7.46%	8.59%
Range (c)			
High	16/50	19/50	25/50
Low	0/50	3/49	7/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks; no hepatoblastomas have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C4b. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN MALE $B6C3F_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
N,N-Dimethylaniline	3/50	0/50	3/50
Ampicillin trihydrate	0/50	0/50	0/50
Penicillin VK	2/46	1/46	3/46
TOTAL	5/146 (3.4%)	1/146 (0.7%)	6/146 (4.1%)
SD (b)	3.10%	1.26%	3.62%
Range (c)			
High	3/50	1/46	3/46
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	(d) 30/2,033 (1.5%)	9/2,033 (0.4%)	(d) 39/2,033 (1.9%)
SD (b)	2.38%	0.87%	2.68%
Range (c)			
High	4/46	1/45	4/46
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two papillomas, NOS

TABLE C4c. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
N,N-Dimethylaniline	6/50	1/50	7/50
Ampicillin trihydrate	1/50	5/50	6/50
Penicillin VK	10/50	0/50	10/50
TOTAL	17/150 (11.3%)	6/150 (4.0%)	23/150 (15.3%)
SD (b)	9.02%	5.29%	4.16%
Range (c)			
High	10/50	5/50	10/50
Low	1/50	0/50	6/50
Overall Historical Incidence			
TOTAL	243/2,084 (11.7%)	117/2,084 (5.6%)	349/2,084 (16.7%)
SD (b)	6.20%	3.79%	6.90%
Range (c)			
High	14/49	6/50	17/49
Low	1/50	0/50	2/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle 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)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, suppurative			1 (2%)
Ulcer, acute	1 (2%)		
Inflammation, acute/chronic	4 (8%)		2 (4%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal		1 (2%)	1 (2%)
Inflammation, chronic diffuse	1 (2%)	2 (4%)	
Parasitism	6 (12%)		2 (4%)
Acanthosis	5 (10%)		
*Subcutaneous tissue	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		
Inflammation, pyogranulomatous	1 (2%)		
Fibrosis	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(50)	(50)
Foreign body, NOS	5 (10%)		1 (2%)
Vegetable foreign body		1 (2%)	1 (2%)
Inflammation, serous	2 (4%)	2 (4%)	3 (6%)
Inflammation, suppurative	9 (18%)	10 (20%)	12 (24%)
Infection, fungal			1 (2%)
Foreign material, NOS	23 (46%)	31 (62%)	29 (58%)
#Nose	(50)	(50)	(50)
Polyp, inflammatory	1 (2%)		
#Nasal mucosa	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Inflammation, acute/chronic	8 (16%)	5 (10%)	9 (18%)
Inflammation, chronic focal	4 (8%)	2 (4%)	6 (12%)
Infection, fungal	1 (2%)		
Degeneration, hyaline	17 (34%)	26 (52%)	27 (54%)
Polyp, inflammatory	3 (6%)		
#Nose/respiratory region	(50)	(50)	(50)
Hyperplasia, focal	5 (10%)	9 (18%)	7 (14%)
Metaplasia, squamous			1 (2%)
#Nose/olfactory region	(50)	(50)	(50)
Metaplasia, NOS		2 (4%)	11 (22%)
#Trachea	(48)	(16)	(48)
Lymphocytic inflammatory infiltrate			2 (4%)
Inflammation, acute focal			1 (2%)
#Lung/bronchus	(50)	(50)	(49)
Inflammation, acute/chronic	3 (6%)	3 (6%)	1 (2%)
Degeneration, hyaline	1 (2%)		
#Lung/bronchiole	(50)	(50)	(49)
Vegetable foreign body		1 (2%)	1 (2%)
Inflammation, active chronic			1 (2%)
Hyperplasia, epithelial	3 (6%)	11 (22%)	14 (29%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM (Continued)			
#Lung	(50)	(50)	(49)
Emphysema, alveolar	1 (2%)		
Atelectasis		1 (2%)	
Congestion, NOS		4 (8%)	
Hemorrhage			1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		5 (10%)
Inflammation, interstitial	1 (2%)	2 (4%)	
Bronchopneumonia, acute		1 (2%)	
Bronchopneumonia, chronic			1 (2%)
Foreign material, NOS			2 (4%)
Hemosiderosis			1 (2%)
Alveolar macrophages	2 (4%)	1 (2%)	6 (12%)
Hyperplasia, alveolar epithelium			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukocytosis, NOS			1 (2%)
Hematopoiesis			1 (2%)
*Blood	(50)	(50)	(50)
Leukocytosis, neutrophilic	2 (4%)		
#Bone marrow	(50)	(15)	(50)
Hyperplasia, diffuse	1 (2%)		1 (2%)
Hyperplasia, erythroid	3 (6%)		2 (4%)
Hyperplasia, granulocytic	10 (20%)	4 (27%)	7 (14%)
#Spleen	(50)	(29)	(50)
Inflammation, granulomatous	1 (2%)		
Hemosiderosis		1 (3%)	1 (2%)
Depletion, lymphoid		2 (7%)	4 (8%)
Hyperplasia, reticulum cell	1 (2%)		
Hyperplasia, lymphoid	3 (6%)		4 (8%)
Hematopoiesis	7 (14%)	2 (7%)	3 (6%)
#Lymph node	(49)	(19)	(46)
Hyperplasia, plasma cell		1 (5%)	
#Mandibular lymph node	(49)	(19)	(46)
Congestion, NOS	2 (4%)		1 (2%)
Hemosiderosis			1 (2%)
Hyperplasia, diffuse	2 (4%)		
Hyperplasia, lymphoid	10 (20%)	2 (11%)	3 (7%)
Hematopoiesis			1 (2%)
#Mediastinal lymph node	(49)	(19)	(46)
Hemorrhage		1 (5%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)
#Pancreatic lymph node	(49)	(19)	(46)
Hemorrhage	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
#Mesenteric lymph node	(49)	(19)	(46)
Congestion, NOS	23 (47%)	3 (16%)	15 (33%)
Hemorrhage			2 (4%)
Angiectasis	1 (2%)		
Histiocytosis	1 (2%)	1 (5%)	3 (7%)
Erythrophagocytosis	1 (2%)		
Hyperplasia, lymphoid	6 (12%)	1 (5%)	6 (13%)
Hematopoiesis	10 (20%)	4 (21%)	8 (17%)
#Inguinal lymph node	(49)	(19)	(46)
Inflammation, chronic diffuse	1 (2%)		
Hyperplasia, lymphoid	9 (18%)		2 (4%)
#Lung	(50)	(50)	(49)
Leukocytosis, NOS	1 (2%)		1 (2%)
#Myocardium	(50)	(23)	(50)
Plasmacytosis	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Liver	(50)	(49)	(50)
Leukocytosis, NOS	2 (4%)		
Hematopoiesis	3 (6%)	1 (2%)	1 (2%)
#Peyer's patch	(50)	(22)	(50)
Hyperplasia, lymphoid		1 (5%)	
#Jejunum	(50)	(22)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Ileum	(50)	(22)	(50)
Hyperplasia, lymphoid			1 (2%)
#Thymus	(24)	(11)	(19)
Ultimobranchial cyst	3 (13%)	1 (9%)	1 (5%)
Cyst, NOS	1 (4%)		
Necrosis, focal		2 (18%)	
Necrosis, diffuse		1 (9%)	
Necrosis, zonal		1 (9%)	
Atrophy, diffuse	12 (50%)	5 (45%)	8 (42%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
Periarteritis	1 (2%)		1 (2%)
#Mesenteric lymph node	(49)	(19)	(46)
Lymphangiectasis	1 (2%)		
#Heart	(50)	(23)	(50)
Periarteritis	2 (4%)		
#Base of heart	(50)	(23)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Heart/atrium	(50)	(23)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Left atrium	(50)	(23)	(50)
Thrombosis			1 (2%)
#Myocardium	(50)	(23)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Fibrosis, focal	1 (2%)		
Necrosis, focal		1 (4%)	1 (2%)
#Cardiac valve	(50)	(23)	(50)
Thrombus, fibrin	1 (2%)		
#Tricuspid valve	(50)	(23)	(50)
Melanin	1 (2%)		
#Mitral valve	(50)	(23)	(50)
Inflammation, acute/chronic	1 (2%)		
#Aortic valve	(50)	(23)	(50)
Hemorrhagic cyst	1 (2%)		1 (2%)
*Coronary artery	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
*Pulmonary artery	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Prostate	(49)	(21)	(48)
Thrombosis, NOS			1 (2%)
DIGESTIVE SYSTEM			
*Hard palate	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
*Tooth	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
Dysplasia, NOS	7 (14%)		3 (6%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Salivary gland	(50)	(25)	(49)
Lymphocytic inflammatory infiltrate	26 (52%)	6 (24%)	23 (47%)
Degeneration, lipoid	2 (4%)		
Cytoplasmic vacuolization	1 (2%)		
Atrophy, diffuse	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Liver	(50)	(49)	(50)
Congestion, acute	1 (2%)	1 (2%)	
Granuloma, NOS	2 (4%)		
Necrosis, focal	6 (12%)	7 (14%)	4 (8%)
Necrosis, diffuse	1 (2%)		
Infarct, NOS		1 (2%)	
Metamorphosis, fatty		1 (2%)	
Basophilic cyto change		1 (2%)	
Eosinophilic cyto change	1 (2%)	1 (2%)	4 (8%)
Pleomorphism	1 (2%)	1 (2%)	3 (6%)
Syncytial alteration	4 (8%)	19 (39%)	36 (72%)
Hyperplasia, focal		1 (2%)	2 (4%)
Angiectasis	1 (2%)		1 (2%)
#Hepatic capsule	(50)	(49)	(50)
Fibrosis, multifocal			1 (2%)
#Intrahepatic bile duct	(50)	(49)	(50)
Hyperplasia, focal			1 (2%)
#Liver/centrilobular	(50)	(49)	(50)
Congestion, NOS		2 (4%)	1 (2%)
Necrosis, NOS		1 (2%)	1 (2%)
Cytoplasmic vacuolization	2 (4%)	4 (8%)	
#Liver/periportal	(50)	(49)	(50)
Cytoplasmic vacuolization	1 (2%)	1 (2%)	
*Gallbladder	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	5 (10%)		2 (4%)
Degeneration, hyaline	1 (2%)		
Crystals, NOS	1 (2%)		
#Pancreas	(50)	(19)	(48)
Hemorrhage			1 (2%)
Lymphocytic inflammatory infiltrate	2 (4%)		
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)	1 (5%)	2 (4%)
Atrophy, focal		1 (5%)	
#Pancreatic duct	(50)	(19)	(48)
Inflammation, focal	1 (2%)		
Lymphocytic inflammatory infiltrate			4 (8%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	6 (12%)		5 (10%)
#Pancreatic acinus	(50)	(19)	(48)
Inflammation, chronic focal			1 (2%)
Atrophy, focal	6 (12%)		4 (8%)
Atrophy, diffuse		1 (5%)	1 (2%)
*Colonic lumen	(50)	(50)	(50)
Hemorrhage			1 (2%)
#Glandular stomach	(50)	(49)	(50)
Congenital malformation, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute/chronic	2 (4%)	2 (4%)	
Necrosis, focal	1 (2%)		
Hyperplasia, epithelial		1 (2%)	
#Forestomach	(50)	(49)	(50)
Ulcer, NOS	2 (4%)	5 (10%)	4 (8%)
Inflammation, acute/chronic	6 (12%)	7 (14%)	4 (8%)
Inflammation, chronic focal	2 (4%)	4 (8%)	5 (10%)
Erosion	1 (2%)	1 (2%)	
Hyperplasia, epithelial	16 (32%)	15 (31%)	24 (48%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Jejunum	(50)	(22)	(50)
Polyp, NOS	1 (2%)		
#Ileum	(50)	(22)	(50)
Amyloidosis	1 (2%)		
#Large intestine	(50)	(20)	(49)
Hemorrhage			1 (2%)
Parasitism			1 (2%)
*Rectum	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Mineralization	1 (2%)	4 (8%)	1 (2%)
Lymphocytic inflammatory infiltrate	6 (12%)	1 (2%)	4 (8%)
Pyelonephritis, acute			1 (2%)
Inflammation, acute/chronic			1 (2%)
Glomerulonephritis, chronic	3 (6%)	2 (4%)	2 (4%)
Infarct, NOS			1 (2%)
Pigmentation, NOS		1 (2%)	
#Kidney/capsule	(50)	(50)	(50)
Fibrosis, focal		1 (2%)	
Hyperplasia, focal	1 (2%)		
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS	3 (6%)	2 (4%)	2 (4%)
Multiple cysts		1 (2%)	
#Perirenal tissue	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Kidney/glomerulus	(50)	(50)	(50)
Amyloidosis	1 (2%)		
#Kidney/tubule	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Cast, NOS			1 (2%)
Degeneration, NOS	23 (46%)	8 (16%)	15 (30%)
Necrosis, diffuse		10 (20%)	
Metamorphosis, fatty			1 (2%)
Pigmentation, NOS			3 (6%)
Hyperplasia, atypical	1 (2%)		2 (4%)
*Ureter	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Urinary bladder	(50)	(23)	(47)
Edema, NOS	2 (4%)		3 (6%)
Lymphocytic inflammatory infiltrate	15 (30%)	2 (9%)	8 (17%)
Inflammation, acute diffuse			1 (2%)
Inflammation, acute/chronic			1 (2%)
Pigmentation, NOS			1 (2%)
#Urinary bladder/submucosa	(50)	(23)	(47)
Inflammation, focal		1 (4%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(47)	(13)	(42)
Cyst, NOS	1 (2%)		1 (2%)
Hyperplasia, focal	3 (6%)	1 (8%)	
#Adrenal/capsule	(49)	(46)	(45)
Ectopia	1 (2%)	2 (4%)	2 (4%)
Inflammation, acute/chronic			1 (2%)
Hyperplasia, focal	40 (82%)	26 (57%)	34 (76%)
#Adrenal cortex	(49)	(46)	(45)
Cyst, NOS		1 (2%)	
Hypertrophy, focal	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, focal	4 (8%)	5 (11%)	3 (7%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(49)	(46)	(45)
Hyperplasia, focal			1 (2%)
#Thyroid	(45)	(16)	(44)
Thyroglossal duct cyst	4 (9%)	1 (6%)	3 (7%)
Follicular cyst, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)		
Hyperplasia, focal			1 (2%)
Hyperplasia, follicular cell	1 (2%)		
#Thyroid follicle	(45)	(16)	(44)
Colloid cyst	2 (4%)		
Inflammation, acute focal	2 (4%)		
Hyperplasia, papillary			1 (2%)
#Parathyroid	(33)	(12)	(23)
Ectopia	2 (6%)		
Cyst, NOS	1 (3%)		
Multiple cysts	1 (3%)		
#Pancreatic islets	(50)	(19)	(48)
Hyperplasia, focal	10 (20%)	2 (11%)	7 (15%)
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)	2 (4%)	
Dilatation/ducts	1 (2%)		1 (2%)
Cyst, NOS		3 (6%)	
Lymphocytic inflammatory infiltrate	1 (2%)		
Abscess, NOS		2 (4%)	
Inflammation, active chronic	3 (6%)	1 (2%)	
Inflammation, acute/chronic	3 (6%)		
Inflammation, chronic	2 (4%)	3 (6%)	
Inflammation, chronic focal	5 (10%)		6 (12%)
Inflammation, pyogranulomatous	1 (2%)		
Atrophy, cystic	5 (10%)		6 (12%)
Atrophy, diffuse	2 (4%)		
#Prostate	(49)	(21)	(48)
Lymphocytic inflammatory infiltrate	17 (35%)	1 (5%)	10 (21%)
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic			1 (2%)
Hyperplasia, focal	3 (6%)		3 (6%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, cystic	1 (2%)		
Angiectasis		1 (2%)	
#Testis	(50)	(24)	(50)
Hyperplasia, interstitial cell	7 (14%)		6 (12%)
#Testis/tubule	(50)	(24)	(50)
Degeneration, NOS	1 (2%)		
Atrophy, focal	2 (4%)		1 (2%)
Atrophy, diffuse	2 (4%)		
*Epididymis	(50)	(50)	(50)
Mineralization	1 (2%)		
Lymphocytic inflammatory infiltrate	3 (6%)		2 (4%)
Inflammation, granulomatous			1 (2%)
Inflammation, granulomatous focal	1 (2%)		1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Brain/meninges	(50)	(23)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
#Lateral ventricle	(50)	(23)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Brain	(50)	(23)	(50)
Inflammation, suppurative		1 (4%)	
#Brain/thalamus	(50)	(23)	(50)
Mineralization	9 (18%)	6 (26%)	9 (18%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	
Inflammation, suppurative	1 (2%)		
Inflammation, acute diffuse		1 (2%)	
Inflammation, acute/chronic	1 (2%)	1 (2%)	2 (4%)
*Eyeball, tunica vasculosa	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
*Eye/retina	(50)	(50)	(50)
Atrophy, diffuse			1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract			1 (2%)
*Eye/conjunctiva	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Foreign body, NOS	1 (2%)		1 (2%)
Vegetable foreign body			1 (2%)
Inflammation, suppurative	1 (2%)		
Inflammation, acute	2 (4%)		
Hyperplasia, focal		1 (2%)	
*Harderian gland	(50)	(50)	(50)
Perivascular cuffing	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		
*Ankle joint	(50)	(50)	(50)
Ankylosis			9 (18%)
*Tarsal joint	(50)	(50)	(50)
Ankylosis	8 (16%)	4 (8%)	3 (6%)
*Muscle of leg	(50)	(50)	(50)
Necrosis, focal			1 (2%)
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Hemorrhage	1 (2%)		
*Mediastinum	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Necrosis, fat			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic			1 (2%)
Necrosis, focal	1 (2%)		
Necrosis, fat	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES (Continued)			
*Epicardium	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
Inflammation, acute focal	1 (2%)		
*Mesentery	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, granulomatous focal		1 (2%)	
ALL OTHER SYSTEMS			
Neck			
Inflammation, acute fibrinous			1
Inflammation, active chronic			1
Inflammation, pyogranulomatous			1
Adipose tissue			
Inflammation, acute/chronic		1	
Inflammation, granulomatous			1
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		1	

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

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle 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)
Keratoacanthoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		2 (4%)	
Fibrosarcoma		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(48)	(47)
Hepatocellular carcinoma, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)	5 (10%)	13 (28%)
Alveolar/bronchiolar carcinoma	1 (2%)	4 (8%)	3 (6%)
Fibrosarcoma, metastatic		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)		1 (2%)
Malignant lymphoma, undifferentiated type	1 (2%)	3 (6%)	1 (2%)
Malignant lymphoma, lymphocytic type	1 (2%)	4 (8%)	1 (2%)
Malignant lymphoma, histiocytic type	1 (2%)		
Malignant lymphoma, mixed type	3 (6%)	2 (4%)	1 (2%)
*Skin	(50)	(50)	(50)
Mast cell tumor	1 (2%)		
#Spleen	(49)	(36)	(47)
Malignant lymphoma, undifferentiated type		1 (3%)	
#Inguinal lymph node	(48)	(22)	(42)
Mast cell sarcoma	1 (2%)		
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma, uncertain primary or meta	1 (2%)		
#Spleen	(49)	(36)	(47)
Hemangiosarcoma	2 (4%)		
#Uterus	(50)	(50)	(48)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(48)	(47)
Squamous cell carcinoma, metastatic			1 (2%)
Hepatocellular adenoma	1 (2%)	22 (46%)	21 (45%)
Hepatocellular carcinoma	3 (6%)	3 (6%)	1 (2%)
Sarcoma, NOS	1 (2%)		
Endometrial stromal sarcoma, metastatic			1 (2%)
Hepatoblastoma		1 (2%)	2 (4%)
#Gastric serosa	(50)	(48)	(47)
Fibrosarcoma, metastatic			1 (2%)
#Forestomach	(50)	(48)	(47)
Squamous cell papilloma	2 (4%)	8 (17%)	5 (11%)
Squamous cell carcinoma		1 (2%)	1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney/capsule	(50)	(49)	(48)
Squamous cell carcinoma, metastatic			1 (2%)
#Kidney/pelvis	(50)	(49)	(48)
Fibrosarcoma, metastatic		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(46)	(42)
Adenoma, NOS	11 (24%)	7 (15%)	3 (7%)
#Adrenal/capsule	(46)	(47)	(47)
Squamous cell carcinoma, metastatic			1 (2%)
Fibrosarcoma, metastatic			1 (2%)
#Adrenal medulla	(46)	(47)	(47)
Pheochromocytoma		1 (2%)	
#Thyroid	(46)	(18)	(42)
Follicular cell adenoma	1 (2%)		
Follicular cell carcinoma		1 (6%)	
#Pancreatic islets	(50)	(22)	(47)
Islet cell adenoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		1 (2%)
*Clitoral gland	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
#Uterus	(50)	(50)	(48)
Histiocytic sarcoma			1 (2%)
Endometrial stromal polyp		1 (2%)	
Endometrial stromal sarcoma			2 (4%)
#Ovary	(47)	(31)	(44)
Papillary cystadenoma, NOS		2 (6%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)		
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Osteoma		1 (2%)	
BODY CAVITIES			
*Pleura	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Fibrosarcoma			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	12	23	20
Moribund sacrifice	1	4	7
Terminal sacrifice	37	19	21
Dosing accident		1	2
Accidentally killed, nda		3	
TUMOR SUMMARY			
Total animals with primary tumors**	27	35	35
Total primary tumors	38	71	60
Total animals with benign tumors	18	29	30
Total benign tumors	20	47	43
Total animals with malignant tumors	15	20	15
Total malignant tumors	16	24	17
Total animals with secondary tumors##		3	4
Total secondary tumors		4	7
Total animals with tumors uncertain-- benign or malignant	1		
Total uncertain tumors	1		
Total animals with tumors-- uncertain primary or metastatic	1		
Total uncertain tumors	1		

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: VEHICLE CONTROL

ANIMAL NUMBER	0404	0411	0412	0430	0220	0443	0001	0223	0228	0331	0335	0332	0338	0002	0003	0004	0005	0006	0007	0008	0009	0110	0111	0113	0114
WEEKS ON STUDY	0007	0551	0699	0699	0777	0881	0991	0993	0993	0995	1002	1033	1033	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor															X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar carcinoma														X											
Trachea	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X					X										
Lymph nodes	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell sarcoma																									
Thymus	−	−	−	−	−	−	−	−	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma											X			X											
Sarcoma, NOS												X													
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma											X														
Small intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X					X		X	X		X				
Adrenal	+	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	−	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																			X						
Parathyroid	−	−	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	+	+	−	+	+	+	−	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma			X																						
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	+	N	N	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Ovary	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																							X		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma, uncertain primary or metastatic										X															
Malignant lymphoma, NOS		X																							
Malignant lymphoma, undifferentiated type																									
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, histiocytic type				X																					
Malignant lymphoma, mixed type																		X							

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0115	0116	0117	0118	0119	0121	0122	0124	0125	0126	0127	0129	0133	0134	0136	0137	0139	0142	0144	0145	0146	0147	0148	0149	0150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mast cell tumor																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	47
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mast cell sarcoma																						X				1
Thymus	+	–	+	+	+	+	+	–	+	–	–	+	+	–	–	+	+	+	–	+	+	–	–	+	–	28
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																								X		1
Hepatocellular carcinoma																	X									3
Sarcoma, NOS																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X																						2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS						X	X		X			X								X		X				11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell adenoma																										1
Parathyroid	+	–	–	+	–	+	–	+	–	+	–	–	–	–	+	–	+	–	+	+	+	–	+	–	–	24
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS											X															1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma						X																				1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																						X				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	*50
Hemangiosarcoma, unc prim or meta																										1
Malignant lymphoma, NOS																										1
Malignant lymphoma, undiffer type																						X				1
Malignant lymphoma, lymphocytic type									X																	1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type		X														X										3

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: LOW DOSE

ANIMAL NUMBER	0171	0191	0211	0401	0233	0335	0004	0055	0266	0377	0488	0333	0455	0114	0332	0341	0227	0289	0299	0300	0204	0443	0381	0111	0433
WEEKS ON STUDY	0004	0044	0077	0099	0188	0661	0744	0744	0744	0766	0788	0800	0811	0844	0877	0887	0888	0888	0888	0888	0900	0900	0911	0933	0933
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	N
Sarcoma, NOS																					X				
Fibrosarcoma						X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic													X												
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic						X																			
Trachea	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	−	−	−
Nasal cavity	−	−	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, undifferentiated type																									
Lymph nodes	+	−	+	−	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	−	+	+	+	−	+
Thymus	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	−	+	−	+	−	+	+	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+
Hepatocellular adenoma							X												X		X		X		
Hepatocellular carcinoma													X											X	
Hepatoblastoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	N	N	N	+	N	N	N	N	N	+	N	+	N	+	+	+	+	N	N	N
Pancreas	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−	−
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	−	−	−
Stomach	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Squamous cell papilloma									X													X			
Squamous cell carcinoma																									
Small intestine	+	−	+	+	+	+	+	+	−	−	−	−	+	+	+	−	+	−	+	+	+	+	−	−	−
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic						X																			
Urinary bladder	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Adenoma, NOS																X									
Adrenal	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	−	−	+	+	+	+	+	+	+	+	−	−	+	−	−	−	+	+	+	+	−	−	−
Follicular cell carcinoma																									
Parathyroid	−	−	−	−	−	+	+	+	+	+	+	−	−	+	−	−	−	−	−	+	+	+	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	N	+	N	N	+	N	+	+	+	+	N	N	N	+	N	N	+	+	+	N	N	N
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
Squamous cell carcinoma																							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	−	
Papillary cystadenoma, NOS										X															
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	−	−
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	N	N	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N
Osteoma																									
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
Alveolar/bronchiolar carcinoma, invasive																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type																									
Malignant lymphoma, lymphocytic type																						X			X
Malignant lymphoma, mixed type																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	01 15	04 42	00 06	05 50	00 08	04 47	00 01	00 02	00 03	00 07	00 09	01 10	01 12	01 13	01 16	01 18	02 22	02 24	02 25	03 31	03 36	03 39	04 41	04 46	04 49	TOTAL TISSUES TUMORS
WEEKS ON STUDY	09 4	09 4	09 5	09 7	10 1	10 1	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	+	+	N	N	N	N	N	N	N	N	N	+	+	N	N	N	N	N	N	+	N	+	N	N	*50
Sarcoma, NOS			X																							2
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma		X			X				X			X							X						5
Alveolar/bronchiolar carcinoma										X			X								X			X		4
Fibrosarcoma, metastatic																										1
Trachea	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	17
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	−	+	+	+	+	+	−	+	−	+	−	−	−	−	−	+	+	−	−	+	−	−	+	−	−	36
Malignant lymphoma, undiffer type					X																					1
Lymph nodes	−	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−	+	−	−	−	−	−	+	−	−	22
Thymus	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
CIRCULATORY SYSTEM																										
Heart	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	21
DIGESTIVE SYSTEM																										
Salivary gland	−	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	19
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma		X					X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	22
Hepatocellular carcinoma					X																					3
Hepatoblastoma																								X		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	−	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	22
Esophagus	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	19
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma				X	X					X					X					X				X	8
Squamous cell carcinoma																		X								1
Small intestine	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	16
Large intestine	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	21
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	49
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	49
Fibrosarcoma, metastatic																										1
Urinary bladder	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	22
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS		X		X					X			X		X			X									7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma																			X							1
Thyroid	−	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	18
Follicular cell carcinoma																								X		1
Parathyroid	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	11
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
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
Squamous cell carcinoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp							X																			1
Ovary	+	+	−	−	−	−	−	+	−	+	−	+	−	+	+	−	−	+	−	−	+	−	+	−	−	31
Papillary cystadenoma, NOS																							X			2
NERVOUS SYSTEM																										
Brain	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	22
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	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
Alveolar/bronchiolar carcinoma, inv																					X					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undiffer type				X													X	X								3
Malignant lymphoma, lymphocytic type						X													X							4
Malignant lymphoma, mixed type																				X					X	2

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN: HIGH DOSE

ANIMAL NUMBER	0022	0044	0042	0005	0023	0008	0039	0003	0047	0049	0048	0046	0001	0036	0110	0038	0009	0026	0045	0037	0113	0115	0118	0020	0033
WEEKS ON STUDY	015	027	030	064	069	070	075	077	080	080	081	082	086	090	091	091	092	093	094	095	096	096	096	096	096
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X	X		X						X	X			
Alveolar/bronchiolar carcinoma													X												
Fibrosarcoma, metastatic																									
Trachea	+	+	+	+	+	–	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	–	+	+	+	+	+	–	+	A	A	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Thymus	+	+	+	+	+	+	–	–	A	A	–	+	–	+	+	+	–	–	–	–	+	–	–	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Hepatocellular adenoma																X			X			X	X	X	X
Hepatocellular carcinoma																									
Endometrial stromal sarcoma, metastatic						X																			
Hepatoblastoma																									
Bile duct	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	N	N	N	N	N	N	N	+	+	N	+	N	+	+	+	N	N	+	+	+	N
Pancreas	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	–	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																									
Fibrosarcoma, metastatic																	X								
Small intestine	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Urinary bladder	+	+	+	–	+	–	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	–	+	–	+	+	A	A	–	–	+	+	+	+	–	+	+	+	+	–	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Fibrosarcoma, metastatic																	X								
Thyroid	–	+	+	+	+	–	+	–	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	+	+	–	+	–	+	–	A	A	–	+	+	–	–	–	+	–	+	+	–	+	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	+	N	+	N	+	N	N	+	+	+
Adenocarcinoma, NOS																X									
Uterus	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Endometrial stromal sarcoma						X																			
Ovary	+	+	+	–	–	+	+	–	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	A	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma																	X								
Malignant lymphoma, NOS														X											
Malignant lymphoma, undifferentiated type																			X						
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	040	041	002	043	004	006	007	011	012	014	016	017	019	021	024	025	027	028	029	030	031	032	034	035	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	096	096	099	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Keratoacanthoma															X											1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Fibrosarcoma																								X		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar adenoma	X		X			X			X	X		X		X							X					13
Alveolar/bronchiolar carcinoma				X		X																				3
Fibrosarcoma, metastatic																								X		1
Trachea	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	42
Thymus	−	−	+	+	+	+	+	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	−	−	−	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic			X																							1
Hepatocellular adenoma	X	X			X		X		X	X				X			X	X	X		X	X	X	X	X	21
Hepatocellular carcinoma															X											1
Endometrial stromal sarcoma, meta																										1
Hepatoblastoma							X														X					2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma			X													X					X		X	X		5
Squamous cell carcinoma			X																							1
Fibrosarcoma, metastatic																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic			X																							1
Urinary bladder	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenoma, NOS																X					X			X		3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic			X																							1
Fibrosarcoma, metastatic																										1
Thyroid	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	42
Parathyroid	−	+	−	−	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+	−	+	+	+	29
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma											X															1
Endometrial stromal sarcoma							X																			2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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
Fibrosarcoma																										1
Malignant lymphoma, NOS																										1
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type																		X								1
Malignant lymphoma, mixed type				X																						1

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle Control	120 mg/kg	240 mg/kg
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	9.6%	4.8%
Terminal Rates (c)	0/37 (0%)	0/19 (0%)	1/21 (5%)
Week of First Observation		61	104
Life Table Tests (d)	P=0.301	P=0.070	P=0.387
Incidental Tumor Tests (d)	P=0.492	P=0.299	P=0.387
Cochran-Armitage Trend Test (d)	P=0.378		
Fisher Exact Test (d)		P=0.121	P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (e)	1/50 (2%)	5/48 (10%)	13/47 (28%)
Adjusted Rates (b)	2.7%	23.0%	43.3%
Terminal Rates (c)	1/37 (3%)	3/19 (16%)	6/21 (29%)
Week of First Observation	104	94	82
Life Table Tests (d)	P<0.001	P=0.017	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.040	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.093	P<0.001
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (e)	1/50 (2%)	4/48 (8%)	3/47 (6%)
Adjusted Rates (b)	2.7%	21.1%	11.5%
Terminal Rates (c)	1/37 (3%)	4/19 (21%)	1/21 (5%)
Week of First Observation	104	104	86
Life Table Tests (d)	P=0.097	P=0.038	P=0.161
Incidental Tumor Tests (d)	P=0.153	P=0.038	P=0.350
Cochran-Armitage Trend Test (d)	P=0.229		
Fisher Exact Test (d)		P=0.168	P=0.285
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (e)	2/50 (4%)	9/48 (19%)	14/47 (30%)
Adjusted Rates (b)	5.4%	42.3%	45.9%
Terminal Rates (c)	2/37 (5%)	7/19 (37%)	6/21 (29%)
Week of First Observation	104	94	82
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.002	P=0.002
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.021	P<0.001
Hematopoietic System: Malignant Lymphoma, Undifferentiated Type			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	2.7%	18.7%	3.1%
Terminal Rates (c)	1/37 (3%)	2/19 (11%)	0/21 (0%)
Week of First Observation	104	97	94
Life Table Tests (d)	P=0.379	P=0.045	P=0.668
Incidental Tumor Tests (d)	P=0.587N	P=0.101	P=0.758N
Cochran-Armitage Trend Test (d)	P=0.601		
Fisher Exact Test (d)		P=0.181	P=0.752
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	2.7%	16.0%	4.8%
Terminal Rates (c)	1/37 (3%)	1/19 (5%)	1/21 (5%)
Week of First Observation	104	90	104
Life Table Tests (d)	P=0.404	P=0.057	P=0.630
Incidental Tumor Tests (d)	P=0.574N	P=0.207	P=0.630
Cochran-Armitage Trend Test (d)	P=0.601		
Fisher Exact Test (d)		P=0.181	P=0.752

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	120 mg/kg	240 mg/kg
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	8.1%	10.5%	4.5%
Terminal Rates (c)	3/37 (8%)	2/19 (11%)	0/21 (0%)
Week of First Observation	104	104	101
Life Table Tests (d)	P=0.452N	P=0.576	P=0.525N
Incidental Tumor Tests (d)	P=0.365N	P=0.576	P=0.394N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	7/50 (14%)	10/50 (20%)	4/50 (8%)
Adjusted Rates (b)	17.0%	40.8%	14.3%
Terminal Rates (c)	5/37 (14%)	5/19 (26%)	1/21 (5%)
Week of First Observation	51	90	90
Life Table Tests (d)	P=0.502	P=0.039	P=0.525N
Incidental Tumor Tests (d)	P=0.236N	P=0.187	P=0.245N
Cochran-Armitage Trend Test (d)	P=0.236N		
Fisher Exact Test (d)		P=0.298	P=0.263N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.7%	0.0%	0.0%
Terminal Rates (c)	2/37 (5%)	0/19 (0%)	0/21 (0%)
Week of First Observation	95		
Life Table Tests (d)	P=0.088N	P=0.256N	P=0.217N
Incidental Tumor Tests (d)	P=0.053N	P=0.182N	P=0.139N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.122N	P=0.122N
Liver: Hepatocellular Adenoma			
Overall Rates (e)	1/50 (2%)	22/48 (46%)	21/47 (45%)
Adjusted Rates (b)	2.7%	91.1%	71.3%
Terminal Rates (c)	1/37 (3%)	17/19 (89%)	13/21 (62%)
Week of First Observation	104	74	91
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (e)	3/50 (6%)	3/48 (6%)	1/47 (2%)
Adjusted Rates (b)	7.8%	10.7%	4.8%
Terminal Rates (c)	2/37 (5%)	0/19 (0%)	1/21 (5%)
Week of First Observation	103	81	104
Life Table Tests (d)	P=0.449N	P=0.397	P=0.527N
Incidental Tumor Tests (d)	P=0.192N	P=0.599N	P=0.394N
Cochran-Armitage Trend Test (d)	P=0.260N		
Fisher Exact Test (d)		P=0.641	P=0.332N
Liver: Hepatoblastoma or Hepatocellular Carcinoma (f)			
Overall Rates (e)	3/50 (6%)	4/48 (8%)	3/47 (6%)
Adjusted Rates (b)	7.8%	15.4%	14.3%
Terminal Rates (c)	2/37 (5%)	1/19 (5%)	3/21 (14%)
Week of First Observation	103	81	104
Life Table Tests (d)	P=0.304	P=0.221	P=0.383
Incidental Tumor Tests (d)	P=0.527	P=0.522	P=0.492
Cochran-Armitage Trend Test (d)	P=0.547		
Fisher Exact Test (d)		P=0.477	P=0.631

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	120 mg/kg	240 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (e)	4/50 (8%)	25/48 (52%)	22/47 (47%)
Adjusted Rates (b)	10.5%	92.0%	74.9%
Terminal Rates (c)	3/37 (8%)	17/19 (89%)	14/21 (67%)
Week of First Observation	103	74	91
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	2/50 (4%)	8/50 (16%)	5/50 (10%)
Adjusted Rates (b)	5.1%	32.3%	22.6%
Terminal Rates (c)	1/37 (3%)	4/19 (21%)	4/21 (19%)
Week of First Observation	102	76	99
Life Table Tests (d)	P=0.046	P=0.004	P=0.055
Incidental Tumor Tests (d)	P=0.157	P=0.035	P=0.133
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.046	P=0.218
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	2/50 (4%)	9/50 (18%)	5/50 (10%)
Adjusted Rates (b)	5.1%	36.8%	22.6%
Terminal Rates (c)	1/37 (3%)	5/19 (26%)	4/21 (19%)
Week of First Observation	102	76	99
Life Table Tests (d)	P=0.044	P=0.002	P=0.055
Incidental Tumor Tests (d)	P=0.148	P=0.015	P=0.133
Cochran-Armitage Trend Test (d)	P=0.209		
Fisher Exact Test (d)		P=0.026	P=0.218
Anterior Pituitary Gland: Adenoma			
Overall Rates (e)	11/46 (24%)	7/46 (15%)	3/42 (7%)
Adjusted Rates (b)	29.6%	30.7%	14.3%
Terminal Rates (c)	10/36 (28%)	4/18 (22%)	3/21 (14%)
Week of First Observation	103	87	104
Life Table Tests (d)	P=0.159N	P=0.429	P=0.155N
Incidental Tumor Tests (d)	P=0.076N	P=0.546N	P=0.115N
Cochran-Armitage Trend Test (d)	P=0.022N		
Fisher Exact Test (d)		P=0.216N	P=0.030N
All Sites: Benign Tumors			
Overall Rates (a)	18/50 (36%)	29/50 (58%)	30/50 (60%)
Adjusted Rates (b)	44.7%	96.4%	87.9%
Terminal Rates (c)	15/37 (41%)	18/19 (95%)	17/21 (81%)
Week of First Observation	69	74	82
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P=0.001
Cochran-Armitage Trend Test (d)	P=0.011		
Fisher Exact Test (d)		P=0.022	P=0.014
All Sites: Malignant Tumors			
Overall Rates (a)	15/50 (30%)	20/50 (40%)	15/50 (30%)
Adjusted Rates (b)	35.2%	65.5%	48.5%
Terminal Rates (c)	10/37 (27%)	9/19 (47%)	7/21 (33%)
Week of First Observation	51	61	70
Life Table Tests (d)	P=0.084	P=0.004	P=0.128
Incidental Tumor Tests (d)	P=0.515N	P=0.130	P=0.540N
Cochran-Armitage Trend Test (d)	P=0.542		
Fisher Exact Test (d)		P=0.201	P=0.586

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	120 mg/kg	240 mg/kg
All Sites: All Tumors			
Overall Rates (a)	27/50 (54%)	35/50 (70%)	35/50 (70%)
Adjusted Rates (b)	61.1%	97.1%	92.0%
Terminal Rates (c)	20/37 (54%)	18/19 (95%)	18/21 (86%)
Week of First Observation	51	61	70
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.013	P=0.004	P=0.036
Cochran-Armitage Trend Test (d)	P=0.058		
Fisher Exact Test (d)		P=0.074	P=0.074

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined microscopically at the site
(f) All hepatoblastomas were observed in animals also bearing a hepatocellular adenoma.

TABLE D4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
N,N-Dimethylaniline	4/50	1/50	5/50
Ampicillin trihydrate	0/49	0/49	0/49
Penicillin VK	2/50	1/50	3/50
TOTAL	6/149 (4.0%)	2/149 (1.3%)	8/149 (5.4%)
SD (b)	4.00%	1.15%	5.03%
Range (c)			
High	4/50	1/50	5/50
Low	0/49	0/49	0/49
Overall Historical Incidence			
TOTAL	102/2,088 (4.9%)	56/2,088 (2.7%)	156/2,088 (7.5%)
SD (b)	4.01%	2.41%	5.07%
Range (c)			
High	10/50	5/50	(d) 15/50
Low	0/50	0/50	0/49

(a) Data as of May 12, 1988, for studies of at least 104 weeks; no hepatoblastomas have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second highest: 9/50

TABLE D4b. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
N,N-Dimethylaniline	2/50	0/50	2/50
Ampicillin trihydrate	0/47	0/47	0/47
Penicillin VK	5/44	0/44	5/44
TOTAL	7/141 (5.0%)	0/141	7/141 (5.0%)
SD (b)	5.76%	0.00%	5.76%
Range (c)			
High	5/44	0/50	5/44
Low	0/47	0/50	0/47
Overall Historical Incidence			
TOTAL	(d) 32/2,047 (1.6%)	1/2,047 (0.05%)	(d) 33/2,047 (1.6%)
SD (b)	2.77%	1.73%	2.76%
Range (c)			
High	5/44	1/47	5/44
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two papillomas, NOS

TABLE D4c. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
N,N-Dimethylaniline	2/49	2/49	4/49
Ampicillin trihydrate	1/50	1/50	2/50
Penicillin VK	3/50	1/50	4/50
TOTAL	6/149 (4.0%)	4/149 (2.7%)	10/149 (6.7%)
SD (b)	2.00%	1.20%	2.36%
Range (c)			
High	3/50	2/49	4/49
Low	1/50	1/50	2/50
Overall Historical Incidence			
TOTAL	94/2,082 (4.5%)	37/2,082 (1.8%)	131/2,082 (6.3%)
SD (b)	2.86%	1.73%	3.34%
Range (c)			
High	5/50	2/48	7/50
Low	0/50	0/50	0/49

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE D4d. HISTORICAL INCIDENCE OF OVARIAN TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Adenomas or Adenocarcinomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	0/44
Ampicillin trihydrate	0/46
Penicillin VK	0/47
TOTAL	0/137
SD (b)	0.00%
Range (c)	
High	0/47
Low	0/47
Overall Historical Incidence	
TOTAL	(d) 6/1,980 (0.3%)
SD (b)	0.86%
Range (c)	
High	2/47
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two papillary adenomas, three papillary cystadenomas, NOS, and one adenocarcinoma, NOS; one benign mixed tumor was also observed.

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, NOS	1 (2%)		
Inflammation, multifocal		1 (2%)	
Inflammation, acute focal	1 (2%)		1 (2%)
Inflammation, acute/chronic	5 (10%)	1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal			2 (4%)
Inflammation, chronic diffuse	1 (2%)	2 (4%)	1 (2%)
Fibrosis	1 (2%)		
Parasitism	1 (2%)		
Melanin			2 (4%)
Hyperkeratosis	1 (2%)		
Acanthosis	3 (6%)		2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute focal	1 (2%)		
Inflammation, acute necrotizing			1 (2%)
Inflammation, active chronic			1 (2%)
Inflammation, acute/chronic		2 (4%)	1 (2%)
Inflammation, chronic		1 (2%)	
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(45)	(47)
Foreign body, NOS	5 (10%)	2 (4%)	1 (2%)
Vegetable foreign body			1 (2%)
Inflammation, suppurative	21 (42%)	17 (38%)	22 (47%)
Inflammation, acute/chronic		1 (2%)	
Infection, fungal	1 (2%)	1 (2%)	2 (4%)
Foreign material, NOS	26 (52%)	27 (60%)	28 (60%)
#Nasal mucosa	(50)	(45)	(47)
Inflammation, acute/chronic	17 (34%)	9 (20%)	35 (74%)
Inflammation, chronic focal	14 (28%)	13 (29%)	7 (15%)
Degeneration, hyaline	41 (82%)	36 (80%)	34 (72%)
Foreign material, NOS	1 (2%)		
#Nose/respiratory region	(50)	(45)	(47)
Hyperplasia, focal	5 (10%)	2 (4%)	9 (19%)
#Nose/olfactory region	(50)	(45)	(47)
Metaplasia, NOS	5 (10%)	20 (44%)	43 (91%)
*Larynx	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
#Trachea	(47)	(17)	(45)
Hemorrhage			1 (2%)
Lymphocytic inflammatory infiltrate	2 (4%)	1 (6%)	4 (9%)
Inflammation, acute			1 (2%)
#Lung/bronchus	(50)	(48)	(47)
Inflammation, acute/chronic			1 (2%)
#Lung/bronchiole	(50)	(48)	(47)
Inflammation, chronic focal			1 (2%)
Hyperplasia, epithelial	1 (2%)	22 (46%)	34 (72%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM (Continued)			
#Lung	(50)	(48)	(47)
Congestion, NOS		2 (4%)	
Hemorrhage		2 (4%)	1 (2%)
Lymphocytic inflammatory infiltrate	6 (12%)	4 (8%)	6 (13%)
Inflammation, interstitial	2 (4%)	3 (6%)	1 (2%)
Inflammation, acute/chronic		2 (4%)	
Alveolar macrophages	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, alveolar epithelium	1 (2%)		1 (2%)
#Lung/alveoli	(50)	(48)	(47)
Edema, NOS			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukocytosis, NOS			1 (2%)
Hematopoiesis		2 (4%)	1 (2%)
*Blood	(50)	(50)	(50)
Leukocytosis, NOS		1 (2%)	
Leukocytosis, neutrophilic			2 (4%)
#Bone marrow	(49)	(50)	(50)
Fibrosis, focal		1 (2%)	
Fibrosis, multifocal		1 (2%)	
Hyperplasia, granulocytic	9 (18%)	15 (30%)	13 (26%)
#Spleen	(49)	(36)	(47)
Congestion, NOS	1 (2%)		
Hemosiderosis	1 (2%)	4 (11%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)		4 (9%)
Hematopoiesis	4 (8%)	10 (28%)	4 (9%)
#Mandibular lymph node	(48)	(22)	(42)
Congestion, NOS			1 (2%)
Hemosiderosis		1 (5%)	1 (2%)
Hyperplasia, lymphoid	5 (10%)	2 (9%)	1 (2%)
#Cervical lymph node	(48)	(22)	(42)
Inflammation, acute/chronic			1 (2%)
#Bronchial lymph node	(48)	(22)	(42)
Inflammation, acute diffuse			1 (2%)
Hyperplasia, lymphoid			1 (2%)
#Mediastinal lymph node	(48)	(22)	(42)
Hemorrhage	1 (2%)		
Inflammation, acute focal		1 (5%)	
Hyperplasia, lymphoid	1 (2%)		4 (10%)
#Pancreatic lymph node	(48)	(22)	(42)
Hyperplasia, lymphoid		1 (5%)	
#Lumbar lymph node	(48)	(22)	(42)
Hyperplasia, lymphoid		1 (5%)	
Hematopoiesis		1 (5%)	
#Mesenteric lymph node	(48)	(22)	(42)
Congestion, NOS	5 (10%)		
Histiocytosis		1 (5%)	
Hyperplasia, lymphoid	3 (6%)		2 (5%)
Hematopoiesis	1 (2%)		
#Renal lymph node	(48)	(22)	(42)
Angiectasis	1 (2%)		
#Axillary lymph node	(48)	(22)	(42)
Abscess, NOS		1 (5%)	
#Inguinal lymph node	(48)	(22)	(42)
Hyperplasia, lymphoid			3 (7%)
Hematopoiesis			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Liver	(50)	(48)	(47)
Hematopoiesis	2 (4%)	9 (19%)	6 (13%)
#Adrenal	(46)	(47)	(47)
Hematopoiesis	1 (2%)	10 (21%)	
#Thymus	(28)	(4)	(29)
Atrophy, focal			1 (3%)
Atrophy, diffuse	17 (61%)	1 (25%)	11 (38%)
Hyperplasia, lymphoid	1 (4%)		4 (14%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Periarteritis	1 (2%)	1 (2%)	
#Mediastinal lymph node	(48)	(22)	(42)
Lymphangiectasis			1 (2%)
#Myocardium	(50)	(21)	(47)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute		1 (5%)	
Inflammation, chronic focal			1 (2%)
Degeneration, NOS			2 (4%)
Angiectasis			1 (2%)
#Cardiac valve	(50)	(21)	(47)
Endocardiosis			1 (2%)
Melanin		1 (5%)	1 (2%)
#Mitral valve	(50)	(21)	(47)
Melanin	1 (2%)		
Hyperplasia, nodular	1 (2%)		
#Aortic valve	(50)	(21)	(47)
Endocardiosis	1 (2%)		
*Coronary artery	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
Inflammation, necrotizing			1 (2%)
#Liver	(50)	(48)	(47)
Perivasculitis	1 (2%)		
#Ovary	(47)	(31)	(44)
Thrombus, organized		1 (3%)	
DIGESTIVE SYSTEM			
*Hard palate	(50)	(50)	(50)
Inflammation, acute focal	1 (2%)		
#Salivary gland	(47)	(19)	(45)
Lymphocytic inflammatory infiltrate	27 (57%)	4 (21%)	24 (53%)
Metamorphosis, fatty			1 (2%)
Cytoplasmic vacuolization			1 (2%)
Cytomegaly		1 (5%)	
Atrophy, focal		1 (5%)	
#Liver	(50)	(48)	(47)
Compression, NOS			1 (2%)
Lymphocytic inflammatory infiltrate	3 (6%)	3 (6%)	3 (6%)
Inflammation, acute/chronic	3 (6%)	1 (2%)	2 (4%)
Granuloma, NOS		1 (2%)	
Inflammation, granulomatous focal	1 (2%)	1 (2%)	1 (2%)
Necrosis, NOS			1 (2%)
Necrosis, focal	5 (10%)	4 (8%)	2 (4%)
Infarct, NOS		1 (2%)	
Metamorphosis, fatty	1 (2%)		2 (4%)
Cytoplasmic vacuolization			3 (6%)
Basophilic cyto change	1 (2%)		1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(48)	(47)
Focal cellular change			1 (2%)
Eosinophilic cyto change	1 (2%)	3 (6%)	6 (13%)
Pleomorphism		1 (2%)	
Syncytial alteration	1 (2%)		2 (4%)
Hyperplasia, focal		3 (6%)	
#Hepatic capsule	(50)	(48)	(47)
Inflammation, suppurative		1 (2%)	
Fibrosis	1 (2%)		
#Liver/centrilobular	(50)	(48)	(47)
Lymphocytic inflammatory infiltrate		1 (2%)	
Metamorphosis, fatty	1 (2%)		
Cytoplasmic vacuolization		1 (2%)	
*Gallbladder	(50)	(50)	(50)
Cast, NOS	2 (4%)		
Lymphocytic inflammatory infiltrate	4 (8%)	1 (2%)	3 (6%)
Inflammation, acute/chronic			1 (2%)
Hyperplasia, papillary	1 (2%)		
#Bile duct	(50)	(48)	(47)
Cyst, NOS			1 (2%)
#Pancreas	(50)	(22)	(47)
Dilatation/ducts		1 (5%)	
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute/chronic		2 (9%)	
Inflammation, chronic focal	2 (4%)	2 (9%)	1 (2%)
Atrophy, focal		1 (5%)	
#Pancreatic duct	(50)	(22)	(47)
Lymphocytic inflammatory infiltrate	5 (10%)		1 (2%)
Inflammation, chronic focal	6 (12%)		8 (17%)
#Pancreatic acinus	(50)	(22)	(47)
Degeneration, lipoid			1 (2%)
Cytoplasmic vacuolization	1 (2%)		
Focal cellular change			1 (2%)
Atrophy, focal	5 (10%)	2 (9%)	2 (4%)
Atrophy, diffuse	1 (2%)		
Hyperplasia, focal		1 (5%)	2 (4%)
#Glandular stomach	(50)	(48)	(47)
Ulcer, NOS	1 (2%)		
Inflammation, acute/chronic	1 (2%)		1 (2%)
Inflammation, chronic focal		1 (2%)	
Necrosis, focal		1 (2%)	
#Forestomach	(50)	(48)	(47)
Ulcer, NOS	2 (4%)	5 (10%)	4 (9%)
Inflammation, acute/chronic		8 (17%)	2 (4%)
Inflammation, chronic focal	1 (2%)		1 (2%)
Foreign material, NOS		1 (2%)	
Hyperplasia, epithelial	7 (14%)	19 (40%)	13 (28%)
Hyperkeratosis	1 (2%)	1 (2%)	
#Large intestine	(48)	(21)	(48)
Parasitism	2 (4%)		
#Colon	(48)	(21)	(48)
Parasitism		1 (5%)	
URINARY SYSTEM			
#Kidney	(50)	(49)	(48)
Glomerulonephritis, NOS		3 (6%)	
Lymphocytic inflammatory infiltrate	7 (14%)	6 (12%)	7 (15%)
Pyelonephritis, acute		1 (2%)	
Glomerulonephritis, chronic	1 (2%)	3 (6%)	1 (2%)
Metaplasia, osseous	1 (2%)	1 (2%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Kidney/capsule	(50)	(49)	(48)
Ectopia		1 (2%)	
Inflammation, acute/chronic		2 (4%)	
Inflammation, chronic		1 (2%)	
Fibrosis, diffuse			1 (2%)
#Kidney/cortex	(50)	(49)	(48)
Cyst, NOS			1 (2%)
#Kidney/tubule	(50)	(49)	(48)
Cast, NOS		1 (2%)	
Degeneration, NOS	2 (4%)	1 (2%)	1 (2%)
Degeneration, hyaline	1 (2%)		
Nephrosis, NOS		1 (2%)	
Necrosis, focal	2 (4%)	1 (2%)	
Inclusion, nuclear	1 (2%)		
*Ureter	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
#Urinary bladder	(47)	(22)	(44)
Edema, NOS			4 (9%)
Lymphocytic inflammatory infiltrate	16 (34%)	7 (32%)	25 (57%)
Inflammation, acute diffuse		1 (5%)	
#Urinary bladder/mucosa	(47)	(22)	(44)
Cytoplasmic change, NOS	1 (2%)		
#Urinary bladder/serosa	(47)	(22)	(44)
Inflammation, chronic	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(46)	(42)
Cyst, NOS	1 (2%)	1 (2%)	
Hyperplasia, focal	13 (28%)	7 (15%)	5 (12%)
Angiectasis	3 (7%)		
#Adrenal/capsule	(46)	(47)	(47)
Ectopia	3 (7%)	2 (4%)	3 (6%)
Inflammation, acute/chronic		1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
Hyperplasia, focal	41 (89%)	43 (91%)	42 (89%)
Hyperplasia, diffuse	2 (4%)	1 (2%)	3 (6%)
#Adrenal cortex	(46)	(47)	(47)
Cyst, NOS			1 (2%)
Metamorphosis, fatty	1 (2%)		
Hypertrophy, focal			1 (2%)
Hypertrophy, diffuse	1 (2%)		
Hyperplasia, focal	3 (7%)		3 (6%)
#Adrenal medulla	(46)	(47)	(47)
Hyperplasia, focal			1 (2%)
#Periadrenal tissue	(46)	(47)	(47)
Lymphocytic inflammatory infiltrate	2 (4%)		1 (2%)
#Thyroid	(46)	(18)	(42)
Thyroglossal duct cyst	3 (7%)	1 (6%)	5 (12%)
Lymphocytic inflammatory infiltrate	4 (9%)		3 (7%)
Hyperplasia, follicular cell	5 (11%)		
#Thyroid follicle	(46)	(18)	(42)
Thyroglossal duct cyst		1 (6%)	
Colloid cyst	2 (4%)		
Inflammation, acute			1 (2%)
Degeneration, NOS	2 (4%)		2 (5%)
Hyperplasia, papillary	1 (2%)		
Hyperplasia, cystic			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Parathyroid	(24)	(11)	(29)
Ectopia	1 (4%)		
Ultimobranchial cyst			1 (3%)
Lymphocytic inflammatory infiltrate	1 (4%)		
#Pancreatic islets	(50)	(22)	(47)
Hyperplasia, focal	2 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Mineralization	1 (2%)		
Dilatation/ducts	3 (6%)		
Lymphocytic inflammatory infiltrate	2 (4%)		5 (10%)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		
Hyperplasia, focal	2 (4%)		
Hyperplasia, diffuse	1 (2%)		
Hyperplasia, cystic	4 (8%)		1 (2%)
*Mammary duct	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Clitoral gland	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Inflammation, suppurative			1 (2%)
Inflammation, acute/chronic			1 (2%)
Inflammation, granulomatous			1 (2%)
Atrophy, cystic			1 (2%)
#Uterus	(50)	(50)	(48)
Dilatation, NOS	6 (12%)	2 (4%)	7 (15%)
Cyst, NOS	1 (2%)		
Inflammation, suppurative	4 (8%)	3 (6%)	3 (6%)
Abscess, NOS	1 (2%)	3 (6%)	
Inflammation, acute/chronic	1 (2%)		2 (4%)
Angiectasis	1 (2%)		2 (4%)
Metaplasia, squamous			1 (2%)
#Uterine serosa	(50)	(50)	(48)
Inflammation, acute/chronic		1 (2%)	
#Uterus/endometrium	(50)	(50)	(48)
Hyperplasia, cystic	38 (76%)	23 (46%)	29 (60%)
#Endometrial gland	(50)	(50)	(48)
Metaplasia, squamous	1 (2%)		
#Ovary	(47)	(31)	(44)
Cyst, NOS	7 (15%)	6 (19%)	6 (14%)
Multiple cysts	3 (6%)		
Parovarian cyst	1 (2%)		
Hemorrhage	1 (2%)		
Hemorrhagic cyst	2 (4%)	1 (3%)	3 (7%)
Abscess, NOS		6 (19%)	
Inflammation, acute/chronic		1 (3%)	
Inflammation, chronic diffuse			2 (5%)
Hemosiderosis	2 (4%)		
Atrophy, brown	6 (13%)	2 (6%)	6 (14%)
Angiectasis	1 (2%)		1 (2%)
#Mesovarium	(47)	(31)	(44)
Cyst, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate	6 (13%)		7 (16%)
Inflammation, acute diffuse			1 (2%)
Inflammation, acute/chronic		3 (10%)	1 (2%)
Inflammation, chronic diffuse	1 (2%)		
#Ovary/follicle	(47)	(31)	(44)
Hemorrhage	1 (2%)		1 (2%)
Hemorrhagic cyst	2 (4%)		1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Brain/meninges	(50)	(22)	(47)
Lymphocytic inflammatory infiltrate	2 (4%)		1 (2%)
#Brain	(50)	(22)	(47)
Mineralization		1 (5%)	
Hemorrhage			1 (2%)
Inflammation, acute focal			1 (2%)
#Brain/thalamus	(50)	(22)	(47)
Mineralization	10 (20%)	4 (18%)	9 (19%)
*Facial nerve	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	1 (2%)		
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	1 (2%)		1 (2%)
*Eye/conjunctiva	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)		
*Nasolacrimal duct	(50)	(50)	(50)
Foreign body, NOS	1 (2%)	1 (2%)	
Inflammation, suppurative	2 (4%)	2 (4%)	2 (4%)
Inflammation, active chronic	1 (2%)		
Inflammation, acute/chronic			1 (2%)
*Harderian gland	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy	17 (34%)	2 (4%)	12 (24%)
*Maxilla	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		
*Tibia	(50)	(50)	(50)
Fibrous osteodystrophy	2 (4%)		
*Knee joint	(50)	(50)	(50)
Inflammation, acute diffuse		1 (2%)	
*Tarsal joint	(50)	(50)	(50)
Ankylosis	1 (2%)		
*Muscle of thorax	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
BODY CAVITIES			
*Body cavities	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
*Thoracic cavity	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
*Mediastinum	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, acute focal			1 (2%)
Inflammation, acute diffuse		1 (2%)	
Abscess, NOS		2 (4%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZOFURAN (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Abdominal cavity (Continued)	(50)	(50)	(50)
Inflammation, acute/chronic		2 (4%)	2 (4%)
Inflammation, chronic diffuse	1 (2%)		
Adhesion, NOS		1 (2%)	
Adhesion, fibrous	1 (2%)		
Necrosis, fat	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Inflammation, chronic suppurative		1 (2%)	
*Pleura	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal		1 (2%)	
*Mesentery	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Necrosis, fat			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation with fibrosis			1 (2%)
Fibrous osteodystrophy	1 (2%)		1 (2%)
Neck			
Hemorrhage	2		
Inflammation, acute focal		1	
Inflammation, pyogranulomatous			1
Adipose tissue			
Inflammation, acute/chronic		1	
Broad ligament			
Inflammation, acute/chronic			1
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	1	1	
Autolysis/necropsy/histology performed			2

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

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

Methods

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

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) MHV (6 mo)	MHV (mouse hepatitis virus) (12,18 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6,12 mo)	RCV (rat coronavirus) Sendai (18 mo)	

Results

Results are presented in Table E1.

TABLE E1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	10/10	PVM
	1/10	RCV
12	10/10	PVM
	10/10	RCV
18	9/9	PVM
	9/9	Sendai
	9/9	RCV
MICE		
6	10/10	PVM
12	9/10	PVM
	2/10	MHV
18	4/6	PVM
	6/6	Sendai
	1/6	MHV

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.

APPENDIX F

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

Pelleted Diet: January 1981 to February 1983

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

TABLE F1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE F2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE F3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.97 ± 0.93	22.7-26.3	23
Crude fat (percent by weight)	5.02 ± 0.45	4.2-5.7	23
Crude fiber (percent by weight)	3.41 ± 0.53	2.9-5.6	23
Ash (percent by weight)	6.39 ± 0.38	5.7-7.1	23
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	10,883 ± 2,705	3,600-18,000	23
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	16.64 ± 2.08	13.0-21.0	23
Riboflavin (ppm)	7.6 ± 0.85	6.10-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.23 ± 0.18	0.72-1.63	23
Phosphorus (percent)	0.99 ± 0.12	0.88-1.47	23
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.46 ± 0.12	0.29-0.83	23
Cadmium (ppm)	<0.10		23
Lead (ppm)	1.01 ± 0.75	0.48-3.37	23
Mercury (ppm) (a)	<0.05		23
Selenium (ppm)	0.28 ± 0.07	0.13-0.40	23
Aflatoxins (ppb) (b)	<10.0		23
Nitrate nitrogen (ppm) (c)	9.60 ± 4.19	3.80-22.0	23
Nitrite nitrogen (ppm) (c)	2.10 ± 1.56	0.40-6.90	23
BHA (ppm) (d)	6.11 ± 4.98	0.04-17.00	23
BHT (ppm) (d)	3.39 ± 2.63	0.90-12.00	23
Aerobic plate count (CFU/g) (e)	38,383 ± 29,013	4,900-88,000	23
Coliform (MPN/g) (f)	35.35 ± 95.28	3.00-460	23
E. coli (MPN/g)	<3.00		23
Total nitrosamines (ppb) (g,h)	3.80 ± 2.66	1.70-9.00	21
Total nitrosamines (ppb) (g,i)	20.18 ± 58.69	1.70-266.20	23
N-Nitrosodimethylamine (ppb) (g, j)	2.66 ± 2.56	0.80-8.30	21
N-Nitrosodimethylamine (ppb) (g,k)	18.99 ± 58.56	0.80-265.00	23
N-Nitrosopyrrolidine (ppb) (g)	1.19 ± 0.57	0.50-2.90	23
Pesticides (ppm)			
α-BHC (a,l)	<0.01		23
β-BHC (a)	<0.02		23
γ-BHC (a)	<0.01		23
δ-BHC (a)	<0.01		23
Heptachlor (a)	<0.01		23
Aldrin (a)	<0.01		23
Heptachlor epoxide (a)	<0.01		23
DDE (a)	<0.01		23
DDD (a)	<0.01		23
DDT (a)	<0.01		23
HCB (a)	<0.01		23
Mirex (a)	<0.01		23
Methoxychlor (m)	<0.05	0.09 (8/26/88)	23
Dieldrin (a)	<0.01		23
Endrin (a)	<0.01		23
Telodrin (a)	<0.01		23
Chlordane (a)	<0.05		23
Toxaphene (a)	<0.1		23
Estimated PCBs (a)	<0.2		23
Ronnel (a)	<0.01		23
Ethion (a)	<0.02		23
Trithion (a)	<0.05		23
Diazinon (a)	<0.1		23
Methyl parathion (a)	<0.02		23
Ethyl parathion (a)	<0.02		23
Malathion (n)	0.09 ± 0.06	0.05-0.27	23
Endosulfan I (a)	<0.01		23
Endosulfan II (a)	<0.01		23
Endosulfan sulfate (a)	<0.03		23

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after July 1981.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) CFU = colony-forming unit
(f) MPN = most probable number
(g) All values were corrected for percent recovery.
(h) Mean, standard deviation, and range exclude two very high values of 117.6 ppb and 266.2 ppb obtained for lots produced on January 26, 1981 and April 27, 1981, respectively.
(i) Mean, standard deviation, and range exclude the very high values listed in footnote (h).
(j) Mean, standard deviation, and range exclude two very high values of 115.0 ppb and 265.0 ppb obtained for lots produced on January 26, 1981 and April 27, 1981, respectively.
(k) Mean, standard deviation, and range include the very high values given in footnote (j).
(l) BHC = hexachlorocyclohexane or benzene hexachloride
(m) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(n) Eleven lots contained more than 0.05 ppm.

APPENDIX G

CHEMICAL CHARACTERIZATION, ANALYSIS, AND DOSE PREPARATION OF BENZOFURAN FOR THE TOXICOLOGY STUDIES

APPENDIX G. CHEMICAL CHARACTERIZATION

Procurement and Characterization of Benzofuran

Benzofuran (98% minimum purity) was obtained as a clear, yellow liquid in two lots from Riches-Nelson, Inc. (Greenwich, CT) (Table G1). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the benzofuran studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the study chemical were identified as benzofuran by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra (Sadtler Standard Spectra) (representative spectra are presented in Figures G1 and G2).

Purity for both lot no. RN7-9-79 and lot no. R092480 was determined by elemental analysis, Karl Fischer water analysis, and gas chromatography.

Gas chromatographic analysis was performed with flame ionization detection and a nitrogen carrier and with a 20% SP2100/0.1% Carbowax 1500 column (system 1) or a 10% Carbowax 20M-TPA column (system 2). Thin-layer chromatography was performed on lot no. RN7-9-79 only. Thin-layer chromatography was carried out at −20° C with silica gel plates (with tetrahydronaphthalene as a reference standard) and a solvent system of *n*-pentane:chloroform (95:5), with visualization at 254 nm and with alkaline permanganate. The cumulative data indicated a purity of approximately 99% for lot no. RN7-9-79. The results of elemental analysis of lot no. RN7-9-79 for carbon were slightly low, those for hydrogen were in agreement with the theoretical value, and those for oxygen were slightly high. Lot no. RN7-9-79 contained 0.054% water. A trace impurity was detected by thin-layer chromatography. Gas chromatography by system 1 indicated six impurities with a combined area of 1.05% relative to the major peak area; system 2 indicated six impurities with a combined relative area of 0.94%. The results of elemental analysis for carbon and hydrogen for lot no. R092480 were in agreement with the theoretical values. Lot no. R092480 contained 0.047% water. Gas chromatography by system 1 indicated two impurities, one before and one after the major peak, with a combined area of 0.16% relative to the major peak area. System 2 indicated two impurities, one before and one after the major peak, with a combined relative area of 0.18%.

Stability studies, performed by gas chromatography with system 1 as described above and with ethylbenzene as an internal standard, indicated that benzofuran was stable as a bulk chemical when kept for 2 weeks, protected from light, at temperatures up to 60° C. Some darkening of the 60° C sample indicated a slight decomposition that was not detected by gas chromatographic analysis. The stability of the bulk chemical during the 2-year studies was monitored by gas chromatography and ultraviolet spectroscopy.

TABLE G1. IDENTITY AND SOURCE OF BENZOFURAN USED IN THE GAVAGE STUDIES

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Number		
RN7-9-79	RN7-9-79	R092480
Date of Initial Use		
10/28/79	1/14/80	1/29/81
Supplier		
Riches-Nelson, Inc. (Greenwich, CT)	Same as 14-d studies	Same as 14-d studies

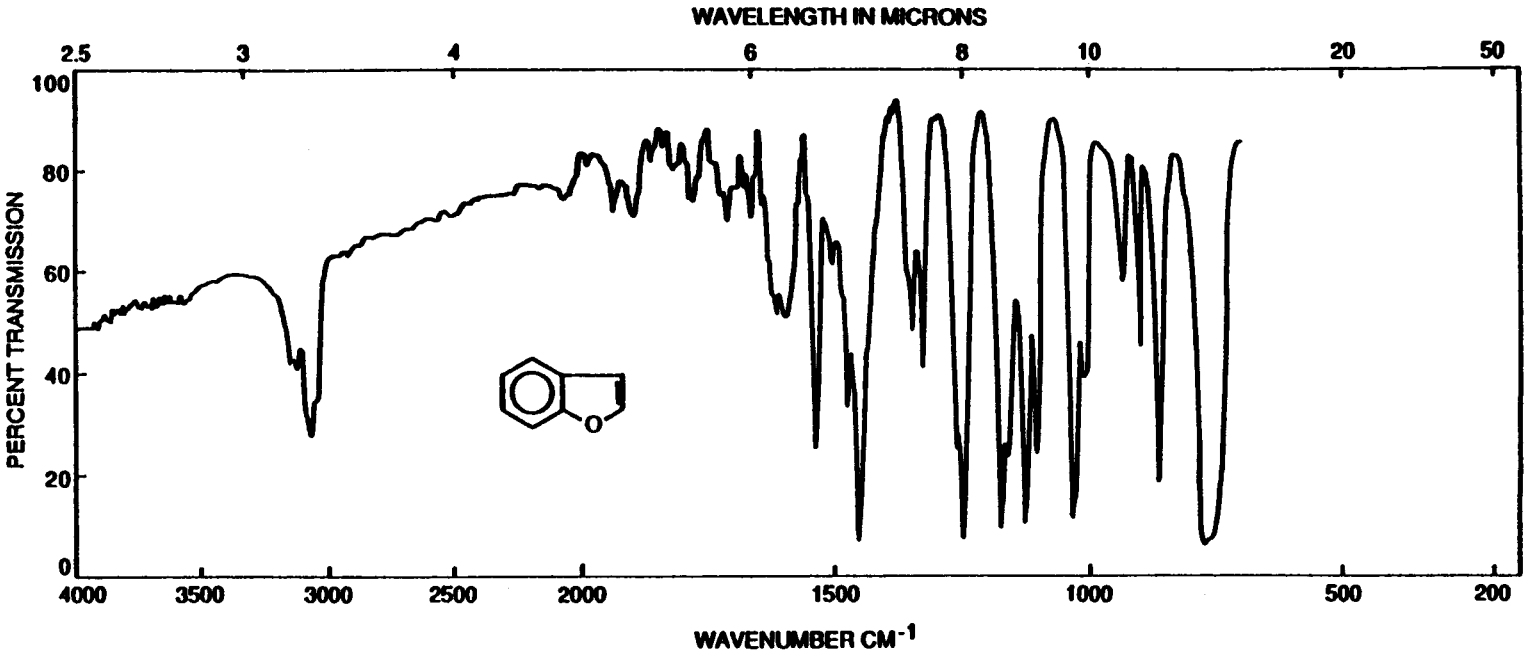

FIGURE G1. INFRARED ABSORPTION SPECTRUM OF BENZOFURAN (LOT NO. RN7-9-79)

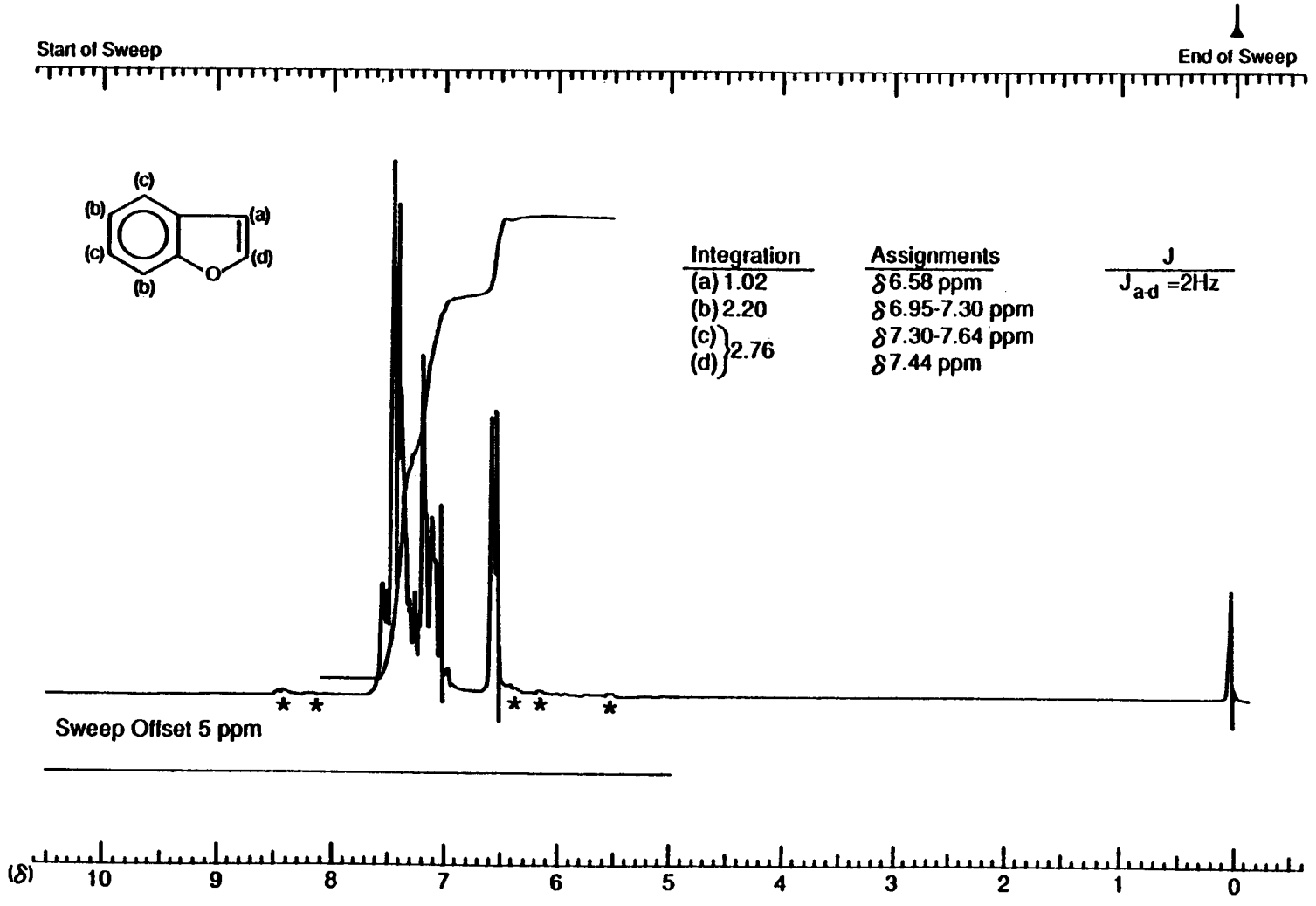

FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF BENZOFURAN (LOT NO. RN7-9-79)

Preparation and Characterization of Dose Mixtures

Benzofuran and corn oil were mixed to give the desired concentrations (Table G2). For the 14-day and 13-week studies, stock solutions were prepared and serial dilutions were made for lower concentrations. The stability of benzofuran in corn oil (2% concentration, w/v) was determined by gas chromatography of methanol extracts with a 10% SP2100 column, flame ionization detection, and undecane as an internal standard. The concentration of benzofuran (20 mg/ ml in corn oil) stored at room temperature in the dark decreased 2.7% and 5.5% after 7 and 14 days, respectively. The same solution stored at 5° C in the dark had losses of 2.5% and 4.4% after 7 and 14 days' storage. These results suggested that gavage solutions of benzofuran in corn oil should be refrigerated and protected from light and should not be kept longer than 7 days. Dose mixtures were stored at about 4° C for no longer than 7 days throughout the studies.

Periodic analysis of formulated benzofuran/corn oil mixtures was conducted at the study laboratory and the analytical chemistry laboratory by extracting dose mixtures and spiked corn oil standards with methanol and determining the absorbance of the extracts at 243 nm. Dose mixtures were analyzed one time during the 13-week studies (Table G3).

During the 2-year studies, the dose mixtures were analyzed at approximately 8-week intervals. For the benzofuran studies, the mixtures were formulated within ±10% of the target concentrations approximately 98% (44/45) of the time throughout the studies (Table G4). The one dose mixture that was out of specifications was prepared at a concentration of 24 mg/ml instead of the required 6 mg/ml. Results of periodic referee analysis performed by the analytical chemistry laboratory indicated excellent agreement with the results from the study laboratory (Table G5).

TABLE G2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF BENZOFURAN

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
Appropriate weight of benzofuran mixed with corn oil by inversion in a volumetric flask for high dose. Lower doses prepared by serial dilution	Appropriate weight of benzofuran mixed with corn oil by magnetic stirrer and stir bar in a volumetric flask for stock solution. Dose mixtures prepared by serial dilution	Appropriate weight of benzofuran mixed with corn oil by magnetic stirrer and stir bar in a volumetric flask
Maximum Storage Time		
1 wk	1 wk	1 wk
Storage Conditions		
~4° C	~4° C	~4° C; daily doses stored in individual vials

TABLE G3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BENZOFURAN (a)

Concentration of Benzofuran in Corn Oil (mg/ml) (b)		Determined as a Percent of Target
Target	Determined	
3.13	3.22	102.9
6.25	6.51	104.2
12.5	13.0	104.0
25	24.2	96.8
50	48.9	97.9
100	102	102

(a) Date mixed: 1/14/80
(b) Results of duplicate analysis

TABLE G4. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN

Date Mixed	Concentration of Benzofuran in Corn Oil for Target Concentration (mg/ml) (a)		
	6	12	24
01/26/81	6.5	11.8	24.0
03/24/81	6.4	12.0	24.0
05/22/81	6.4	12.2	23.7
06/19/81	(b) 24.0	12.0	24.0
07/10/81	5.9	11.2	22.0
09/18/81	5.9	11.4	22.1
11/06/81	5.4	11.5	23.0
01/08/82	6.0	12.0	23.5
02/26/82	6.2	12.1	23.4
04/23/82	6.1	12.3	23.7
06/11/82	5.9	12.1	24.0
09/03/82	5.9	12.6	23.9
10/01/82	5.9	12.1	23.8
11/19/82	6.2	12.1	23.8
01/14/83	6.1	12.0	23.4
Mean (mg/ml)	7.3	12.0	23.5
Standard deviation	4.64	0.36	0.65
Coefficient of variation (percent)	63.6	3.0	2.8
Range (mg/ml)	5.4-24.0	11.2-12.6	22.0-24.6
Number of samples	15	15	15

(a) Results of duplicate analysis
(b) Out of specifications; if this value is excluded, the mean ± standard deviation would be 6.1 ± 0.28 mg/ml.

TABLE G5. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF BENZOFURAN

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
03/24/81	6	6.4	6.4
11/06/81	12	11.5	12.3
04/23/82	24	23.7	24.1
10/01/82	6	5.9	6.3
01/14/83	12	12.0	11.9

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

APPENDIX H

GENETIC TOXICOLOGY

OF BENZOFURAN

APPENDIX H. GENETIC TOXICOLOGY

METHODS

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 1 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants which was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response was considered negative when no increase in revertant colonies was observed after chemical treatment.

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by McGregor et al. (1988) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 0.2 mg/ml. Mouse L5178Y/TK lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

All doses within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 ml of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with the study chemical continued for 4 hours, after which time the medium plus chemical was removed and the cells were resuspended in 20 ml of fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with Tft for selection of Tft-resistant cells ($TK^{+/+}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C under 5% carbon dioxide for 10-12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P < 0.05$) for a chemical to be considered capable of inducing Tft resistance; a single significant response led to an "equivocal" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr et al. (1985). This assay was initially performed

without S9; if a clearly positive response was not obtained, the experiment was repeated with induced S9.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 0.25 mg/ml.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, L-glutamine (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium plus BrdU and colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical; incubation proceeded for an additional 26 hours, with colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; colcemid was added, and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the chromosomal aberration test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the chromosomal aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 100 first-division metaphase cells were scored at each dose for the chromosomal aberration test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

RESULTS

Benzofuran was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in a preincubation protocol at doses up to 1,000 µg/plate in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Haworth et al., 1983; Table H1). Benzofuran induced Tft resistance in mouse L5178Y/TK lymphoma cells treated with doses of 100 µg/ml and greater in the absence of exogenous metabolic activation (S9); this assay was not conducted with S9 (McGregor et al., 1988; Table H2). In cytogenetic tests with cultured CHO cells, benzofuran induced SCEs in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Table H3). The higher doses of benzofuran required a delayed harvest protocol to obtain sufficient metaphase II cells for scoring; significantly increased SCE frequencies were noted with both standard and delayed harvest protocols. No induction of chromosomal aberrations was observed in CHO cells treated with up to 275 µg/ml benzofuran with or without S9 (Table H4).

TABLE H1. MUTAGENICITY OF BENZOFURAN IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	85 ± 6.6	80 ± 6.5	84 ± 6.2	104 ± 1.9	96 ± 10.0	88 ± 7.0
	10	85 ± 4.2	116 ± 27.8	82 ± 3.4	120 ± 8.0	90 ± 10.0	80 ± 7.8
	33.3	85 ± 8.5	77 ± 2.0	90 ± 5.5	117 ± 9.5	88 ± 2.0	81 ± 3.5
	100	72 ± 4.7	65 ± 6.7	75 ± 7.2	110 ± 2.7	91 ± 9.7	105 ± 11.9
	333.3	(c) 55 ± 6.1	77 ± 7.3	84 ± 10.4	103 ± 9.5	88 ± 7.3	89 ± 2.3
	1,000	Toxic	(c) 65 ± 6.9	(c) 42 ± 21.5	Toxic	(c) 36 ± 18.3	(c) 84 ± 3.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		413 ± 8.8	328 ± 33.9	1,383 ± 66.9	2,062 ± 75.0	528 ± 9.3	1,066 ± 12.2
TA1535	0	10 ± 1.3	14 ± 1.2	6 ± 2.5	8 ± 1.3	9 ± 1.5	5 ± 2.0
	10	15 ± 1.2	16 ± 0.7	13 ± 0.9	10 ± 1.8	6 ± 1.7	9 ± 1.5
	33.3	11 ± 2.0	24 ± 3.7	11 ± 2.1	7 ± 0.7	5 ± 0.3	6 ± 0.6
	100	15 ± 3.4	19 ± 2.5	8 ± 2.4	7 ± 0.3	6 ± 1.9	8 ± 0.9
	333.3	9 ± 1.7	19 ± 4.0	6 ± 1.3	6 ± 0.3	4 ± 1.0	6 ± 0.3
	1,000	(c) 4 ± 1.2	(c) 19 ± 1.2	(c) 2 ± 2.0	Toxic	Toxic	(c) 5 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		350 ± 10.4	352 ± 4.8	470 ± 34.0	385 ± 22.7	313 ± 14.2	387 ± 26.3
TA1537	0	7 ± 1.5	6 ± 0.6	7 ± 3.1	8 ± 3.2	9 ± 2.1	6 ± 0.7
	10	4 ± 1.2	7 ± 1.2	6 ± 1.7	6 ± 0.9	8 ± 2.4	8 ± 0.6
	33.3	5 ± 0.6	8 ± 0.7	10 ± 2.8	6 ± 1.5	8 ± 2.6	8 ± 1.9
	100	7 ± 0.7	7 ± 1.7	5 ± 1.5	6 ± 1.2	6 ± 1.0	7 ± 0.7
	333.3	(c) 2 ± 1.2	8 ± 1.5	5 ± 0.7	5 ± 1.0	5 ± 1.0	8 ± 1.0
	1,000	Toxic	(c) 4 ± 0.0	(c) 0 ± 0.0	(c) 1 ± 1.0	Toxic	(c) 9 ± 1.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		124 ± 40.2	156 ± 19.7	445 ± 13.0	385 ± 9.5	235 ± 5.8	461 ± 16.3
TA98	0	28 ± 1.7	20 ± 3.2	24 ± 1.7	21 ± 3.5	35 ± 5.9	22 ± 3.1
	10	23 ± 2.8	20 ± 3.8	39 ± 5.0	23 ± 3.7	35 ± 3.1	23 ± 2.7
	33.3	20 ± 0.9	28 ± 0.9	30 ± 1.5	24 ± 2.6	34 ± 2.1	23 ± 3.0
	100	25 ± 3.2	27 ± 1.2	35 ± 1.3	21 ± 1.5	40 ± 2.6	22 ± 2.6
	333.3	11 ± 1.3	23 ± 5.6	21 ± 2.6	26 ± 4.3	23 ± 2.5	17 ± 1.5
	1,000	(c) 2 ± 2.0	(c) 18 ± 3.0	(c) 3 ± 2.5	(c) 8 ± 4.9	Toxic	(c) 10 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		797 ± 18.8	682 ± 33.7	1,177 ± 53.5	1,361 ± 32.5	326 ± 16.1	787 ± 53.4

(a) Study performed at SRI International. The detailed protocol and data are presented in Haworth et al. (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Slight toxicity
(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE H2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE IN MOUSE L5178Y LYMPHOMA CELLS BY BENZOFURAN (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
Trial 1					
Dimethyl sulfoxide (d)		86.5 ± 8.6	100.0 ± 1.7	200.3 ± 25.4	78.8 ± 10.1
Benzofuran	12.5	95.5 ± 4.5	134.0 ± 3.0	159.5 ± 2.5	55.5 ± 3.5
	25	82.5 ± 0.5	137.0 ± 27.0	198.0 ± 45.0	79.5 ± 17.5
	50	91.0 ± 6.0	130.5 ± 7.5	207.0 ± 10.0	75.5 ± 1.5
	100	85.0 ± 3.0	73.5 ± 12.5	143.0 ± 20.0	56.0 ± 6.0
	(e) 200	90	14	383	142
Methyl methanesulfonate	15	50.0 ± 8.0	43.0 ± 9.0	397.5 ± 45.5	(f) 267.0 ± 10.0
Trial 2					
Dimethyl sulfoxide (d)		93.3 ± 5.2	100.0 ± 2.5	163.5 ± 17.9	58.3 ± 3.9
Benzofuran	50	82.5 ± 10.5	67.0 ± 1.0	141.0 ± 5.0	57.5 ± 5.5
	100	66.5 ± 1.5	28.5 ± 2.5	177.5 ± 2.5	89.0 ± 1.0
	150	38.5 ± 6.5	8.0 ± 2.0	254.5 ± 12.5	(f) 229.5 ± 50.5
	200	Lethal	--	--	--
Methyl methanesulfonate	15	41.5 ± 0.5	25.0 ± 1.0	418.5 ± 50.5	(f) 337.0 ± 34.0
Trial 3					
Dimethyl sulfoxide (d)		98.8 ± 3.7	100.0 ± 3.3	90.8 ± 5.0	30.8 ± 1.5
Benzofuran	100	91.0 ± 16.0	31.5 ± 1.5	160.0 ± 43.0	(f) 57.5 ± 5.5
	125	66.0 ± 7.0	21.5 ± 0.5	149.5 ± 27.5	(f) 75.0 ± 6.0
	150	74.5 ± 7.5	13.5 ± 2.5	229.5 ± 11.5	(f) 103.5 ± 5.5
	175	81.0 ± 3.0	9.5 ± 0.5	325.0 ± 10.0	(f) 134.0 ± 9.0
	200	80.5 ± 8.5	8.5 ± 0.5	327.5 ± 36.5	(f) 136.0 ± 0.0
	225	Lethal	--	--	--
Methyl methanesulfonate	15	29.0 ± 2.0	17.5 ± 1.5	288.5 ± 34.5	(f) 329.5 ± 15.5

(a) Study performed at Inveresk Research International. The experimental protocol and data are presented in detail by McGregor et al. (1988) and follow the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in duplicate, unless otherwise noted; the average for the tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

(b) Mean ± standard error from replicate trials of approximately 1×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.

(c) Mutant fraction (frequency) is a ratio of the Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.

(d) Data presented are for four tests.

(e) Data presented are for one test.

(f) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.

TABLE H3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY BENZOFURAN (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide		50	1,032	461	0.45	9.2	25.5	
Benzofuran	11	50	1,044	496	0.48	9.9	25.5	107.6
	36.7	50	1,033	574	0.56	11.5	25.5	125.0
	110	50	1,042	581	0.56	11.6	25.5	126.1
Mitomycin C	0.001	50	1,034	623	0.60	12.5	25.5	135.9
	0.01	50	104	186	1.79	3.7	25.5	40.2
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,038	490	0.47	9.8	25.7	
Benzofuran	174.9	50	1,027	681	0.66	13.6	(d) 31.0	138.8
	199	50	1,024	691	0.67	13.8	(d) 31.0	140.8
	249.9	50	1,022	703	0.69	14.1	(d) 31.0	143.9
							(d) 31.0	
Mitomycin C	0.001	50	1,034	693	0.67	13.9	25.7	141.8
	0.01	5	103	193	1.87	38.6	25.7	393.9
+S9 (e) Summary: Positive								
Dimethyl sulfoxide		50	1,024	464	0.45	9.3	25.5	
Benzofuran	174.9	50	1,033	616	0.60	12.3	25.5	132.3
	199	50	1,040	581	0.56	11.6	25.5	124.7
	249.9	50	1,033	705	0.68	14.1	(d) 33.0	151.6
Cyclophosphamide	0.3	50	1,032	722	0.70	14.4	25.5	154.8
	2	5	100	168	1.68	33.6	25.5	361.3

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) and (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE H4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY BENZOFURAN (a)

Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
−S9 (b) Harvest time: 20.5 hours (c)					+S9 (d) Harvest time: 10.5 hours				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	2	0.02	2.0		100	4	0.04	3.0
Benzofuran					Benzofuran				
224.0	100	2	0.02	2.0	149.7	100	1	0.01	1.0
248.8	100	6	0.06	4.0	200.8	100	3	0.03	2.0
276.6	100	4	0.04	4.0	249.5	100	9	0.09	2.0
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.062	50	32	0.64	44.0	50	50	30	0.60	36.0

(a) Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) and (d). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) Because of significant chemical-induced cell cycle delay, incubation time prior to addition of colcemid was lengthened to provide sufficient metaphases at harvest.
(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft (October 1988) of NTP Technical Report No. 370 for the 2-year studies of benzofuran in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by quality assurance, resource-support contractors. The audit included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, animal husbandry, room and exposure-chamber environmental conditions, dosing, external masses, mortality, animal identification, and serology.
(3) Body weight and clinical observation data; all data were scanned before individual data for a random 10% sample of animals in each study group were reviewed in detail.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning date of death, disposition code, condition code, tissue accountability, correlation of masses or clinical signs recorded at or near the last inlife observation with gross observations and microscopic diagnoses, consistency of data entry on necropsy record forms, and correlation between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory and residual wet tissues from a random 20% sample of animals in each study group, plus other relevant cases, to evaluate the integrity of individual animal identity and the thoroughness of necropsy and trimming procedure performance.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group, plus animals with less than complete or correct identification, to examine for proper inventory, matching of tissue sections, and preservation.
(8) All microscopic diagnoses for a random 20% sample of animals, plus 100% of the changes in diagnoses made to preliminary pathology tables, to verify their incorporation into the final pathology tables.
(9) The extent of correlation between the data, factual information, and procedures for the 2-year studies as presented in the draft Technical Report and the study records available at the NTP Archives.

Full details about the audit findings are presented in audit reports that are on file at the NIEHS.

Procedures and events for the exposure phase of the studies were documented adequately by the archival records, with the exception that some or all of the records for room air change rate, room light cycle, cleaning agents used, cage filters, bedding type, and corn oil analyses performed were not available at the Archives. Review of the records indicated that protocol procedures for animal care were followed adequately. Records that documented the preparation, analysis, storage, and administration of doses to animals were complete and accurate. Recalculation of approximately 20% of the group mean body weight values in the Technical Report showed all to be correct. The correlation between observations of external masses recorded both during the last few months of life and at necropsy was good (all but one in rats and seven in mice correlated). The date of death recorded at necropsy for each unschdeuled-death animal (162 rats and 142 mice) was supported by the inlife records.

Individual animal identifiers (ears and feet) were present and correct in the residual tissue bags for 71/76 rats and 55/65 mice examined. Review of the entire data trail for the 5 rats and 10 mice with less than complete and correct identifiers indicated that the integrity of individual animal identity had been maintained, but ears and feet had not been saved in all cases. A total of 14 untrimmed potential lesions (1 involved spleen) were found in the wet tissues of 76 rats examined, and 11 (7 involved stomach and uterus) were found in those of 65 mice examined. Intestinal segments were incompletely opened for 12/76 rats and 51/76 mice; however, there were no apparent untrimmed potential lesions evident by external examination. Each gross observation made at necropsy had a

corresponding microscopic diagnosis, except for 22 noncorrelations in rats. Tissue sections in blocks and on slides matched each other properly. All post-Pathology Working group changes in diagnoses had been incorporated into the final pathology tables. The tumor incidences given in the Technical Report were the same as those in the final pathology tables in the study records.

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